BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

Managing Editor, E. COWLES ANDRUS

Associate Managing Editor, JOHN A. LUETSCHER, JR.

CHARLES R. AUSTRIAN
W. HALSEY BARKER
KENNETH C. BLANCHARD
EDWARD M. HANRAHAN
JOHN EAGER HOWARD
ARNOLD R. RICH

VOLUME LXXXII

BALTIMORE
THE JOHNS HOPKINS PRESS
1948

COPYRIGHT, 1948
BY THE JOHNS HOPKINS PRESS

JAN 20 1948

HOSPITAL LIBRARY

VOLUME 82 NUMBER 1

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

January, 1948

An Anti-Rh Antigen-Antibody Reaction Factor (The Rh Protective Factor). Preliminary Report. ALLAN BLOXSOM AND ROSE MATTHAEI 1

Psychotherapy in General Medical Practice. JOHN C. WHITEHORN 10

The Resistance of the Young Rabbit to the Diabetogenic Effect of Alloxan. CARL SWAN SHULTZ AND JAMES R. DUKE ... 20

Malignant Tumors of the Nasopharynx. THOMAS E. VAN METRE, JR. 42

The Treatment of Miliary Tuberculosis With Promizole. EDITH M. LINCOLN, SAMUEL STONE, AND OLGA R. HOFFMAN 56

Book Reviews 76

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

COPYRIGHT, 1948, BY THE JOHNS HOPKINS PRESS

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, E. COWLES ANDRUS

ASSOCIATE MANAGING EDITOR, JOHN A. LUETSCHER, JR.

EDITORIAL BOARD

Charles R. Austrian
W. Halsey Barker
Kenneth C. Blanchard
Edward M. Hanrahan
John Eager Howard
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2

THE JOHNS HOPKINS PRESS

BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

AN ANTI-Rh ANTIGEN-ANTIBODY REACTION FACTOR (THE Rh PROTECTIVE FACTOR)

Preliminary Report

ALLAN BLOXSOM AND ROSE MATTHAEI

Received for publication July 21, 1947

In a preceding article a report was made on an infant, Baby F. (1), with erythroblastosis fetalis who accidentally received a massive transfusion of Rh-negative blood. Since the course of the hemolytic disease of this newborn infant was so favorably altered by the large transfusion, the possibility that an Rh-negative donor's serum might possess some factor that suppressed or inhibited the Rh antigen-antibody reaction was suggested. If this is true, the serum of Rh-negative donors should be of as much value in transfusions into infants with erythroblastosis fetalis as the Rh-negative red blood cells.

The present study was undertaken to determine, if possible, whether this factor could be demonstrated in Rh-negative blood serums. Accordingly the effects of Rh-negative and Rh-positive serums on the agglutination of Rh-positive cells were studied with commercial Rh-diagnostic serums and with serums containing anti-Rh agglutinins. The commercial testing serum used in this experiment was obtained from the Certified Blood Donor Service in Jamaica, N. Y. The commercial testing serum used in the agglutinations in the included case report was obtained from Dr. J. M. Hill, of the Baylor University Hospital, Dallas, Texas.

Technique for Testing for Rh-Protective Factor

Reagent. Pooled sera (Rh+) of each of the four principal groups, AB, A, B, and O. Pooled cells (Rh+) of each of the four principal groups, AB, A, B, and O. Anti-Rh serum (our preference is the lyophilized serum obtained from the Buchanan Blood Serum and Plasma Center, Dallas, Texas), which is resuspended in 0.9% NaCl solution (normal saline).

Cell suspension. Wash pooled clots of specific type until a heavy suspension of cells is obtained (use saline or Rh+ serum). Centrifuge until cells are loosely packed. If there is any hemolysis, pour off supernatant fluid. However, if cells are so fragile that a second washing is necessary, they cannot be used. Resuspend

cells in type specific Rh + serum (pooled), making a 2–3% suspension. Use one drop (from a 1 ml. pipette) into each tube of series, both tests and controls.

Blood for testing is obtained by venipuncture and placed in a sterile tube. No anticoagulant is used. Blood is allowed to clot. The clear serum is used for the test. The cells are checked for type and Rh factor.

Technic. A series of ten Kahn size tubes is set up for each serum to be tested and another series of the tubes is set up for each control (a control is set up for each type of blood to be tested; i.e., if there are types A and O in the sera to be tested, a control is set up for each. Like series of tubes are set up to check for iso-agglutinins in each serum to be tested. (In case of donors, the single tube test for iso-agglutinins is satisfactory when there is no history of transfusion or pregnancy.)

For Anti-Rh Antigen-Antibody Reaction Factor

Tube #	1	2	3	4	5	6	7	8	9	10
	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.
Unknown Rh-serum.....	0.15	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Anti-Rh serum.....	0.05									

(Mix and transfer 0.1 cc. to Tube 2. Mix and transfer 0.1 cc. of tube 2 to tube 3, etc., throughout the series, this making the dilutions 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512, 1:1024, 1:2048.)

Cell suspension as described above. Add 1 drop from 1 ml. pipette to each tube.

For Control	1	2	3	4	5	6	7	8	9	10
	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.
Rh + Serum (group specific).....	0.15	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Anti-Rh Serum 0.05 cc. (Mix and transfer as above, to successive tubes.) Cell suspension as described above. Add 1 drop from 1 ml. pipette to each tube.

Test for iso-agglutinins. Set up series of tubes as for the control, using type specific pooled serum but use 0.05 cc. of serum to be tested IN PLACE OF the commercial Anti-Rh serum in the first tube. Proceed as in other series of tests.

Allow to stand at room temperature overnight OR incubate in 37° waterbath for 45 minutes. If room temperature drops as much as 15° below 37°, during the over night incubation period, place racks of tubes in waterbath for 15 minutes before centrifuging.

Centrifuge tubes at approximately 2500 rpm for 4–5 minutes. Read promptly. Tilt tube gently (any rough shaking of tube will completely mask a ± reaction). Read before a frosted light (Kahn or microscope lights are satisfactory). Readings are + (large, distinct aggregations of cells, with no outflow of single cells); ± (smaller aggregations of cells, with some dispersion of cells), − (no aggregation of

Hospital
Gift
Dr Carl V. Weller

cells). If reading is a weak ±, reading may be facilitated by noting aggregate at bottom of the tube. ± shows a rough, irregular edged circle, while − shows a smooth circle with single cells flowing from the sides.

STUDY 1

In order to provide controls for the various phases of this problem, the titer of the commercial Rh-diagnostic serum was determined on Rh-positive cells of stock group O and stock group A blood as well as on the blood of Baby F. (group A), dilutions being made with isotonic solution of sodium chloride. The results of the control studies are shown in table 1.

The commercial anti-Rh testing serum showed titers of 1:64 with the three groups of Rh-positive cells used in the following studies.

TABLE 1

Titer of Commercial Testing Anti-Rh Serum

	DILUTIONS OF ANTI-Rh TESTING SERUM							
	1:4	1:8	1:12	1:16	1:24	1:32	1:48	1:64
Testing with red blood cells:								
Rh-positive (O).....	+	+	+	+	+	+	±	±
Rh-positive (A).....	+	+	+	+	+	+	±	±
Rh-positive (A) (Baby F)..	+	+	+	+	+	+	+	+

(All dilutions were made with isotonic solution of sodium chloride.)

STUDY 2

This study was done on the serum of the donor, Mr. B., who supplied the blood for the massive transfusion previously reported. It was done to determine, if possible, the existence of any anti-Rh antigen-antibody reaction factor in his blood. The results are shown in table 2.

When the commercial anti-Rh testing serum was variously diluted with the serum of Mr. B., there was evidence of anti-Rh antigen-antibody reaction factor activity in agglutinations of and above 1:10 but complete inhibition of agglutination in dilutions of and above 1:40. When isotonic solution of sodium chloride was used as the diluent, agglutination occurred in dilutions of 1:64.

STUDY 3

This study consisted of examining the effects of various Rh serums from Rh-positive and Rh-negative donors on the red blood cells of

TABLE 2

Anti-Rh Antigen-Antibody Reaction Factor Titer of Serum of Donor Mr. B. for Infant F.

	DILUTIONS OF ANTI-Rh TESTING SERUM						
	1:5	1:10	1:15	1:20	1:30	1:40	1:60
Testing with red blood cells of infant F. Rh-positive (A)	+	±	±	±	±	−	−
(All dilutions were made with serum of donor Mr. B. for infant F.)							
Control shown in table 1	+	+	+	+	+	+	+

TABLE 3

Effect of Incubation of Various Rh-Negative and Rh-Positive Blood Serums on the Rh-Positive Cells of an Infant with Erythroblastosis Fetalis

	DILUTIONS OF ANTI-Rh TESTING SERUM						
	1:5	1:10	1:15	1:20	1:30	1:40	1:60
Testing with Rh-positive (A) cells of infant F. Using serum of Rh-negative donor:							
Mrs. P.	+	±	±	±	−	−	−
Mrs. C.	+	+	±	±	−	−	−
Mr. B.	+	±	±	±	±	−	−
Using serum of Rh-positive donor:							
"x"	+	+	+	−	−	−	−
"y"	+	+	+	+	+	+	+
"z"	+	+	+	+	±	±	±

(All dilutions were made with serum from Rh-negative and Rh-positive donors.)

Baby F., who received the massive transfusion. The results are shown in table 3.

The most striking result apparent from table 3 is the fact that Rh-negative blood serums were much more effective in inhibiting agglutination than Rh-positive blood serums. The red blood cells from

Baby F. used in this study sixty days after the massive transfusion probably contain some Rh-negative red blood cells. The serum of the donor Mr. B., who gave the massive transfusion, is shown to be effective in preventing agglutination of the infant's cells by potent commercial anti-Rh testing serum. This fact, of course, suggests the

TABLE 4

Effect of Incubation of Various Rh-Negative and Rh-Positive Blood Serums on Rh-Positive Cells Tested with Commercial Rh Testing Serum

	DILUTIONS OF ANTI-Rh TESTING SERUM						
	1:5	1:10	1:15	1:20	1:30	1:40	1:60
Testing with							
Rh-positive (A) red blood cells using serum of Rh-negative (A) donors:							
Mrs. P.	+	±	±	−	−	−	−
Mrs. C.	±	±	−	−	−	−	−
Mr. B.	−	−	−	−	−	−	−
Rh-positive (O) red blood cells using serum of Rh-negative (O) donors:							
Mrs. H.	±	±	±	±	±	±	−
Mr. McD.	−	−	−	−	−	−	−
Rh-positive (A) red blood cells using serum of Rh-positive (A) donors:							
"x"	±	±	±	±	±	±	±
"y"	+	+	+	+	+	+	+
"z"	+	+	+	+	+	+	±
Rh-positive (O) red blood cells using serum of Rh-positive (O) donors:							
"a"	±	±	±	±	−	−	−
"b"	±	±	±	±	±	±	±

(All dilutions were made with serums of Rh-negative and Rh-positive donors.)

reason for the beneficial results on erythroblastosis fetalis when Rh-negative blood is used for transfusions. It further suggests that there may be a beneficial result or effect on the fetus exposed to anti-Rh agglutinin if that mother during gestation is given serum from Rh-negative donors at regular intervals.

STUDY 4

The effect of Rh-negative and Rh-positive blood serums on agglutinations of Rh-positive cells with the commercial anti-Rh testing serum was studied. The results are shown in table 4.

There is a rather noticeable difference between the degree of inhibition of agglutination with the use of serums from Rh-negative donors and the inhibition produced by Rh-positive serums. One Rh-positive serum ("a") acted somewhat like Rh-negative serum and there is some hereditary evidence that this donor is heterozygous instead of homozygous. A further study is being done on persons whose blood reacts in this fashion, and it may be possible to predict whether an Rh-positive person is heterozygous or homozygous from the presence or absence of the anti-Rh antigen-antibody reaction factor in his serum, as true Rh-positive donors seem to have little or none of this factor in their serums. From table 4 it is evident that the Rh-negative male donors tested, not having received a transfusion, show considerable anti-Rh antigen-antibody reaction factor in their serum.

COMMENT

Rh-negative blood serums, particularly those of males that have been tested, contain an anti-Rh antigen-antibody reaction factor that inhibits the Rh antigen-antibody reaction. The presence of such a factor can furnish an answer to a number of questions about hemolytic disease of the newborn (erythroblastosis fetalis). Such a factor, as will be pointed out later, could be of great value in the treatment and possibly in prevention of this condition.

Levine expressed the opinion that one should expect erythroblastosis fetalis to be a disease exclusively of the fetus, with spontaneous cure at birth. The presence of such an inhibiting Rh antigen-antibody reaction factor circulating in Rh-negative blood and holding this reaction in abeyance or to a minimum until the fetus is removed from its sphere of influence would explain the mechanism in many instances of rapid development of erythroblastosis fetalis shortly after birth.

As has frequently been observed, the titer of the maternal anti-Rh agglutinins is not necessarily proportionate to the severity of the fetal disease. The reason for this lack of correlation between the severity

of the disease in the fetus and the concentration of agglutinins in the mother's blood is stated by Potter to be unknown. The presence of an anti-Rh antigen-antibody reaction factor can explain this phenomenon. Women whose infants are affected with the most severe form of the disease and in whom it is impossible to demonstrate agglutinins may have little or no inhibiting anti-Rh antigen-antibody reaction factor present, so that the infant receives no protection from his mother. In mothers having a high titer and a high neutralizing anti-Rh antigen-antibody reaction factor, the infant may be given considerable protection and be only mildly, if at all, affected.

The presence of this anti-Rh antigen-antibody reaction factor in Rh-negative blood serum and possibly to some extent in heterozygous Rh-positive blood serum further explains why Rh-negative blood is much more effective in transfusions for infants with erythroblastosis fetalis.

Clinical experimental work with mothers given serum from Rh-negative male donors during gestation of expected erythroblastotic infants in an effort to inhibit or minimize the injury to their fetuses will be reported. At the present time the blood of an Rh-negative mother having a normal infant after a previous infant who died of erythroblastosis fetalis has been studied. Anti-Rh agglutinins that were present days before delivery in this mother's blood disappeared twelve hours after delivery of the normal infant. The anti-Rh antigen-antibody reaction factor increased in this mother's blood serum approximately fourfold. Anti-Rh agglutinins were demonstrated also in the normal infant's cord blood, and the anti-Rh antigen-antibody reaction factor was present in the same titer as in the mother's blood serum.

A question may arise as to whether or not the prevention of agglutination of Rh-positive cells in the presence of a potent anti-Rh agglutinin serum is the result of the "blocking anti-bodies" described by Wiener. These "blocking antibodies," or univalent agglutinins, were independently discovered by Race and by Wiener. The "blocking antibodies" combine with their antigen, but the reaction stops at this point in vitro and no agglutination or hemolysis occurs. The presence of these univalent agglutinins can be demonstrated by adding potent anti-Rh-agglutinating serum to a mixture of patient's serum that has

been incubated with group O, Rh-positive cells. If the patient's serum does not contain any "blocking antibodies," strong clumping should now be evident. Should the patient's serum contain "blocking antibodies," the Rh-positive red cells will remain unagglutinated, or the clumping will be weakened. The anti-Rh antigen-antibody reaction factor is different from the "blocking antibodies" because it occurs in the serums of Rh-negative male donors who have received no blood transfusions and obviously could not be sensitized by pregnancy. Second, ten infants with erythroblastosis fetalis have received large transfusions to date from selected Rh-negative male donors with the higher titers of the Rh protective factor for the effect of this factor. The response has been excellent, and all infants have done well, something one would not expect if this protective factor is a "blocking antibody."

The paralleling clinical and laboratory evidence showing the anti-Rh antigen-antibody reaction factor to be a natural protective factor present in the blood of Rh-negative persons is being published. It is suggested, therefore, that this natural Rh-reaction inhibitory factor be called the Rh-protective factor.

The serums of Rh-positive men who from their offspring are known to be heterozygous will be examined for evidence of the anti-Rh antigen-antibody reaction factor. If this is consistently found, it may constitute a simple determining test for the Rh heterozygote.

SUMMARY

1. The serums of the Rh-negative bloods used in the studies of this article have been shown to contain an anti-Rh antigen-antibody reaction factor that inhibits the Rh antigen-antibody reaction.

2. The serums of the Rh-positive bloods used in the studies of this article have been shown to contain no anti-Rh antigen-antibody reaction factor except for the small amount found in one man who is heterozygous.

3. At the present time it is believed that this anti-Rh antigen-antibody reaction factor is a specific inhibiting substance for the Rh reaction. The natural occurrence of this anti-Rh antigen-antibody reaction factor serves as a vital protective means for Rh-negative persons and for infants subject to hemolytic disease of the newborn.

Serum from Rh-positive persons in the few instances tested nullified the inhibiting power of the serum from Rh-negative male donors.

4. The value of both cells and serums of Rh-negative bloods, with, probably, the serums being of greater value for transfusions in infants having erythroblastosis fetalis due to anti-Rh agglutinins, is believed in at present.

5. The males tested in this study showed in their blood serums greater amounts of this anti-Rh antigen-antibody reaction factor, and it is possible that blood used from such donors will be more effective in the treatment of hemolytic disease of the newborn (erythroblastosis fetalis).

6. The prevention of hemolytic disease of the newborn (erythroblastosis fetalis) is an obstetric problem. It is hoped that the use of suitable Rh-negative blood and blood serums at regular intervals before delivery in the light of its inhibitory effect on anti-Rh agglutination in vivo and in vitro, as demonstrated in this article, may result in the salvage of a larger number of those infants.

7. The presence of the anti-Rh antigen-antibody reaction factor in the serums of Rh-positive males may point to the fact that those males are heterozygous.

REFERENCES

1. Bloxsom, A.: Hemolytic Disease of the Newborn (Erythroblastosis Fetalis). Case Report of Infant Receiving a Massive Transfusion of Rh-Negative Blood with Complete Recovery. Am. J. Dis. Children, **72:** 320 (Sept.) 1946.
2. Wiener, A. A.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., Charles Thomas, Publisher, 1943.
3. Levine, P.: The Pathogenesis of Erythroblastosis Fetalis. J. Pediat., **23:** 656 (Dec.) 1943.
4. Potter, E. L.: Present Status of the Rh Factor. Am. J. Dis. Child., **68:** 32 (July) 1944.
5. Bloxsom, A.: Outlook for Infants Receiving Anti-Rh Agglutinins from Isoimmunization of Mothers. Texas State J. Med., **42:** 279 (Aug.) 1946.
6. Wiener, A. S.: A New Test (Blocking Test) for Rh Sensitization. Proc. Soc. Exper. Biol. & Med., **56:** 173 (June) 1944.
7. Race, R. R.: An "Incomplete" Antibody in Human Serum. Nature, London, **153:** 771 (June 24) 1944.
8. Bloxsom, A.: The Rh-Protective Factor. South. Med. J. In press.

PSYCHOTHERAPY IN GENERAL MEDICAL PRACTICE

JOHN C. WHITEHORN

From the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital

Received for publication July 31, 1947

Illnesses of emotional origin—the neuroses and allied disorders—constitute a large part of the ill health for which people seek medical help. Estimates vary, ranging from the neighborhood of one-third of all patients up to two-thirds of all patients, as the proportion of those in whom the most significant cause of ill-health is of emotional or neurotic character. The larger estimates include many who do have some organic pathology which is not considered an adequate explanation for the complaints presented. On the more conservative estimate, about one patient in every three entering a doctor's office needs psychotherapeutic assistance; yet medical education has not prepared physicians well to meet this need, or even in fact to recognize properly the neurotic illnesses at the stages in which they respond best to psychotherapeutic treatment. An attempt is made herein to outline a perspective on the therapeutic possibilities and principles by which the physician may be aided in his treatment of the neuroses and allied forms of illness.

Let us plunge at once into the consideration of a type of neurotic illness familiar to all physicians—the anxiety reaction, or the "jitters." The anxiety reaction may proclaim itself in obvious clinical manifestations of tension, tremulousness, restlessness, moist palms, rapid or irregular action of the heart, and "butterflies" in the stomach, or may be masked behind a patient's complaint of "heart trouble", "stomach trouble" or "thyroid trouble", or it may be half concealed by some once-respectable medical term like neurocirculatory asthenia or shell-shock.

Let us for our purpose suppose that the diagnostic problem is settled—the patient is found to have a neurotic anxiety reaction. The problem is then therapeutic, and this therapeutic problem is in the setting of general medical practice. What help can be given such a patient?

Well, in the general run of medical practice there will be a certain

proportion of patients, a rather small proportion, who spontaneously respond very well when informed that their symptoms are of emotional origin. Such a patient may be aware of a persistent source of uncertainty or worry which can be decisively settled and whose settlement relieves his anxiety.

More commonly, however, the patient is not able without help to understand the personal meaning of his anxiety. He is therefore unable to take decisive action, and so continues in the anxiety state, or he may even get more anxious over the added worry that something is going wrong in his mind about which he can do nothing. Is this a problem about which the general practitioner can do some useful therapy, or is it necessary to call in a psychiatrist, and, if so, where are we to get the tens of thousands of psychiatrists needed? These are pressing problems which come up at once when one faces the issue. Of course you know and I know that the issue is usually not faced. The doctor finds some "suggestive evidence" of possible avitaminosis or endocrinopathy. He embarks upon a series of therapeutic trials, trying to bolster up his own hope, against his better clinical judgment, that this capsule or that injection will somehow do the therapeutic trick. It usually doesn't. This is sometimes known as giving the patient the benefit of the doubt, but that is not the correct way to state it. Unfortunately, when the first flush of suggestive benefit has faded, the patient has usually added another layer of psychopathology to the anxiety reaction,—he has become in some measure hypochondriacal or neurasthenic, confirmed, so to speak, in the pill-taking faith, or goes on to seek surgical intervention, so the still remaining psychotherapeutic task is multiplied in complexity and difficulty.

Let us return then to the question, "Can the general practitioner do some useful psychotherapy in those anxiety reactions which do not promptly cure themselves when reassured as to organic integrity?" Opinions differ on this question. Everyone must admit that there do exist certain rare physicians with remarkable powers of intuitive insight and personal charm who are able to give much support to anxiety-ridden patients. The practical question concerns, however, the more nearly average physician,—the one without this "magic touch." Can he learn to give useful psychotherapy to patients in anxiety states?

My own opinion is, "Yes, but with two important qualifications." First, one has to give some serious study and effort to mastering the intelligible principles of psychotherapy and, second, one needs to establish serious consultative contacts with some other physician or physicians likewise seriously interested in psychotherapy. You will note, and perhaps be surprised at my setting forth the necessity for consultative contacts with another physician. You would perhaps be less surprised if I specified consultative contacts with a well-trained psychiatrist, which would of course be fine. But another general practitioner will do. I wish to return to this consideration later.

The first necessary step for the general practitioner in doing useful psychotherapy is the mastery of some intelligible principles of psychotherapy. This involves a scientific and professional understanding of human nature which has seldom in the past been presented to the physician at the right time, namely, in medical school. The medical schools are, one by one, in varying degree, moving toward a better fulfillment of this obligation. The physicians of the future should be much more adequately informed about personality functions and personality disorders than the physicians of our generation. But it is my obligation to try to say now what constitutes the minimal grasp of principles which the present general practitioner would need to know to undertake psychotherapy.

I do not believe that doctors should attempt to do psychotherapy blindfolded—that is to say, in ignorance of psychopathology and psychodynamics. In considering the treatment of neurotic anxiety reactions, one should have some fairly clear concept as to the nature of this disorder. Like other neurotic illnesses, the anxiety reaction is a symptom of unfinished business,—some internal conflict or issue which the patient has not been able to settle, and which therefore haunts him. I would go further and express my agreement in general with those who say that neurotic anxiety reactions are symptoms of difficulty in managing some inner impulses. This is usually unknown to the patient. The patient commonly believes his anxiety is aroused by circumstances, but that belief just misses the bull's eye. The circumstances arouse certain unacceptable impulses, and the patient's difficulty in handling those impulses is what stirs up the anxiety. I express myself rather dogmatically on this point because my observations and

experiences have convinced me of the general validity of this conception of the anxiety reaction, and I consider it of great strategic importance for therapy. It is not always necessary for success in psychotherapy to know the original cause of the patient's conflict of impulses, but it is a great help to know something of its nature in the individual case, that is to recognize what sort of impulse is aroused by the circumstances and to mobilize the patient's resources for dealing decisively with that sort of impulse.

Not only is the neurotic patient ordinarily ignorant of the nature of the impulses concerned in his anxiety reaction; he doesn't want to know, if he can avoid it, for these impulses are usually of a sort that would shame him. It is just at this point that the emotional nature of the patient-physician relationship has its crucial importance in psychotherapy. People can sometimes endure to take off their concealments and look at themselves in the doctor's presence, in a way they can do in few other situations. If the doctor can stand the view, the patient can too. Some doctors can't stand it,—they are made very uncomfortable by raw human nature. Such a doctor should not try to do psychotherapy. Human nature is not all pretty on the inside. There is a good deal of meanness and low animal nature native to everyone. In recent decades those recesses of human nature concerned with sex have been widely publicized. There is some reason to believe that people in general now have a less sordid view of sex than prevailed a generation ago. Nevertheless, the physician who undertakes to do psychotherapy should be prepared to make the acquaintance of some fairly sordid aspects of human nature, sexual or otherwise. Those who have to steel themselves to endure the sordid revelations of human impulses do not do very good psychotherapy. It seems to require a fairly robust faith in the human race,—a faith which may grow with a doctor's experience, as his knowledge of his patients' lives broadens and deepens. One of the basic principles of psychotherapy is to permit the patient to be straight-forwardly honest about himself. I say "permit" advisedly because I find that physicians often automatically shut off the patient from telling the candid truth because of the overprotective medical tradition.

The parallel to this principle of straightforward candor is for the physician to display interest in, and appreciation for, the patient's

assets and good points. In every medical history designed for psychotherapeutic purposes there should be a section which tells of the patient's best periods and the pattern of the patient's life at those periods. This provides concrete information about the patient's level of personality functioning at its best, but, more significantly, the detailed conversation with the physician about the periods of good functioning may revive afresh some of the constructive and positive personal attitudes which made one function well at that time.

In reading some of the modern psychiatric literature and especially in attending psychiatric movies, the American public has been fascinated by the search for that one childhood incident which was *the cause* for today's neurosis. Well, a great many patients are helped to make very good recoveries without anyone's ever learning *the cause* in this sense. Indeed, it may generally be doubted whether it is proper in most cases, to speak of *the cause* as a single incident, since the crux of a neurosis often lies in a conflict of attitudes or a failure in personality development, which had a long and intricate development without any one specific incident as the cause. What is of much greater importance than to find the cause is to discern the meaning of the symptoms, the motivation, in terms of the issue at stake in the life situation to which the neurosis is the patient's reaction. There are no wholly dependable tricks of the trade which can be relied upon to reveal this meaning when the patient is reluctant or unable to talk. It happens to be true that mute patients—those who do not talk—happen to be a special personal interest of mine, and I have developed certain skills in establishing communication with them, but those skills are not the business of the general practitioner. I do, however, wish to offer one suggestion of considerable value in trying to figure out the meaning to the patient of a life-situation which seems to the physician trivial and inappropriate as the occasion for so much anxiety. That suggestion is to evaluate the level of the patient's emotional maturity, which may be done, approximately, by a suitable interview and history. I do not mean merely to decide that the patient is immature. That is somewhat too general. What I mean is to locate approximately the patient's position on a scale of emotional growth, the principal positions being denoted by the terms infantile, childish, early adolescent, late adolescent and adult. These terms, as I use them, summarize

the level to which the patient's personality has grown in its emotional maturation, rather specifically in regard to dependence and responsibility. For teaching purposes I have defined these terms in the following brief fashion:

Infant level: complacently or petulantly dependent.

Child level: making excuses for self, but expecting perfection in others.

Early Adolescent level: "Independent" of authority but much concerned about contemporaries—badges, cliques, prestige—"showing off"; strenuously adventurous.

Late Adolescent level: Very self-consciously idealistic, or cynical or romantic; sophisticated or sophomoric "line"; radical or extremist in belief but less adventurous in action.

Adult level: More absorbed in work or family than in self-assertion; reconciled to limitations through satisfaction in real achievements; accepting and sharing responsibility without "fuss."

A biographical review and interview which provides the evidence for evaluating the patient's level of emotional maturity generally serves also to reveal attitudes involved in the patient's neurotic reaction to the current life-situation, giving the doctor a fairly clear idea of the emotional meaning of the situation to the patient, even though the patient is still in the dark. Just how well the general practitioner can learn to size up patients' attitudes and the levels of emotional maturity must of course vary with one's insight and experience, and the amount of study and thought given to the matter. It is not wholly a gift. It is a skill that can be developed by exercise.

Granted then that the physician has a certain degree of skill in evaluating people's attitudes in relation to life-situations and the level of maturity, and is thereby equipped to discern the meaning of the patient's neurotic anxiety reaction to a situation seemingly inappropriate, such a physician is, in a fair measure, prepared to undertake psychotherapy, and that psychotherapy will consist largely in the thoughtful and respectful consideration with the patient of how the situation might be met more effectively, not by an ideal person, but by the person who is the patient, using to the best advantage the assets and attitudes which he has shown in periods of good adjustment. When I say consider with the patient, I mean consider, I do not mean

to urge or to exhort, but to consider things together with mutual respect. The doctor need not be excessively humble or passive about this, for in his ordinary quiet and objective way the physician often exerts tremendous personal influence which can be brought to the support of the patient's weakened self-confidence. This personal influence in the patient-physician relationship is the real moving force in psychotherapy. The whole art of psychotherapy depends largely on learning how to exert this special personal influence strategically to the patient's best advantage in finding a better way to meet life-situations. That is why it is important to know something about patients as persons and about the dynamics of neurotic reactions.

This brings me to the second qualification which I specified when I said that the general practitioner could do effective psychotherapy, with two qualifications. The first I have just finished discussing in a general way,—the mastery of a certain knowledge of human nature and the psychodynamics of neuroses. The second qualification was that he should establish serious consultative contacts with some other physician or physicians likewise interested in psychotherapy; and I would like now to consider with you the meaning and purpose of this point. The most active agency in psychotherapy is the emotional relationship and interaction between patient and physician, and I seriously doubt if this rather intensive personal relationship can be employed effectively and yet with professional discretion and judgment unless the physician attempting to do so has a trusted professional colleague to whom he can make objective reports and thereby keep himself objectively oriented.

There has been much discussion in recent years of group psychotherapy. What I am attempting to say now is the converse of ordinary group psychotherapy—namely, that the psychotherapist should be a member of a group numbering at least two who share a common and serious interest in following each other's psychotherapy. They may in this fashion maintain each other's objectivity in the employment of a rather subtle kind of subjective influence—the emotional relationship between patient and physician.

Let me tell you some of the reasons which lead me to emphasize this point. It has been my good fortune to become acquainted in several sections of this country, and in the Army, with a number of

physicians who have become individually interested in psychotherapy and have attempted individualistically to do psychotherapy. The physician attempting to do psychotherapy all on his own, so to speak, is not usually aware of the emotional intensity of the patient's reactions to him until it suddenly erupts explosively, whereupon he over-reacts in a defensive or aggressive way and spoils the whole therapy; or perhaps the doctor himself gets emotionally involved in a way which is not helpful. After a few experiences of these kinds the interested physician usually adopts one or the other of two opposite patterns. Either he becomes so coldly professional and impersonal in attitude as to lose most of the potentiality for effective psychotherapy, or he drifts into a series of intensive personal relationships with patients which cease to have therapeutic value to the patients and which become in effect a special neurosis of the physician. To avoid these two extremes of reaction, nothing is so helpful as the habit of objective report and consultation with another professional associate who has a similar sympathetic but practical interest in psychotherapy.

It is also helpful to point out another reason for consultative contacts to maintain objectivity. The doctor who is unsuccessful in the attempt to exercise his personal influence in psychotherapy suffers a more disturbing personal frustration than when his prescriptions are unsuccessful. This experience is hard to take all alone, but if two or more share each other's experiences in an objective way each knows that the others are also frustrated at times, and consequently does not take his own defeats so much to heart.

We have been considering, in some detail, the considerations which seem to me important and necessary for the physician in general practice to do useful psychotherapy for patients who are in the condition called anxiety reaction.

There is a large group of neurotic illnesses which might be comprehended under the headings of tension states and fatigue states. By and large these are simply cases of anxiety reaction in which the effects of anxiety have come to loom larger than the anxiety itself. The principles of treatment are essentially the same,—to arrive at a sound personal diagnostic formulation through mutually respectful consideration with the patient of his reaction and the life-situation, and to utilize the personal influence of the patient-physician relationship to

provide a corrective and supportive emotional experience, whereby the patient may come to deal with his situation more effectively and maturely.

There is, however, a more complicated level of neurotic illness, which may be more frustrating to one's psychotherapeutic ambitions. I refer now to the neurotic defense mechanisms, such as hysterical conversion, hypochondriasis, circumscribed phobias, and obsessive-compulsive adjustments. Expressed in the broadest terms, these neurotic defense mechanisms may be considered as devices for evading major anxiety reactions by unconscious mechanisms which gain one special sympathy or excuse one from facing intolerable situations. Some of these conditions are very difficult to treat psychotherapeutically, others respond well and promptly. It is not always possible to tell which will respond well. Success in their psychotherapeutic treatment is made more difficult, in general, by the passage of time, by the multiplication of operations and special tests, and by the taking of medicines. In general, the psychotherapy of the neurotic patient with well-established neurotic defense mechanisms is a task for the specialist rather than the general practitioner. One may hope, however, as psychiatric training improves in medical schools, that more and more medical men, even though not specialists in psychiatry, will be able to treat such patients successfully.

There is one special group which I wish to discuss because of its prevalence and general medical importance. I refer now to the group of patients called by Alvarez the "constitutional inadequate." These are persons who are always tired or suffering various aches and pains because they try to live at a level which is beyond their physiological means. In this sense the concept of constitutional inadequacy has a certain validity. In the main I consider it more accurate to pin down at least a large proportion of these cases under the designation of obsessive perfectionists. In other words it has seemed to me that such patients have not been able to be reasonably lenient on themselves because they are driven by neurotically obsessive attitudes. They tend therefore to alternate between a worn-out neurasthenic state in which they are dreadfully tense, irritable and fatigued and have to be inactive, and a state of obsessive overwork which drives them again into the fatigue state. Some of these patients can be saved from what

is a rather miserable pattern of life by psychotherapy directed at the relief of the obsessive mechanism. The general practitioner sees great numbers of these patients, and may be able to help a few by psychotherapy of a fairly blunt and straightforward type designed to relieve the obsessiveness.

In concluding this discussion of psychotherapy in general medical practice, I will summarize the main points by saying that many patients showing anxiety reactions may be aided considerably by psychotherapy which can be done by the general practitioner who is willing to put in a certain amount of hard work to gain an understanding of the matter and who will maintain consultative contacts with a colleague likewise seriously interested. Many patients in tension states can likewise be aided. The prospects are not so good for the psychotherapy of well established neurotic defense reactions by the general practitioner, but it does seem potentially useful for him to attempt psychotherapy on a very numerous group of patients who are neurotically driven by obsessive perfectionism to exertions beyond their physiological capacity to sustain.

The development of a moderately successful skill in psychotherapy should be a considerable source of gratification to the practitioner in providing a feeling of decent competence for dealing with that one-third or more of his patients whose primary medical need is for psychotherapy. The insight into human nature, which is a by-product of psychotherapeutic success, enriches one's professional life through a very interesting and gratifying appreciation of the constructive potentialities of human beings.

THE RESISTANCE OF THE YOUNG RABBIT TO THE DIABETOGENIC EFFECT OF ALLOXAN

CARL SWAN SHULTZ AND JAMES R. DUKE

From the Department of Pathology, The Johns Hopkins University School of Medicine

Received for Publication July 22, 1947

INTRODUCTION

Following the discovery by Dunn, Sheehan, and McLetchie (8) that the ureide of mesoxalic acid, alloxan, injected into the rabbit in doses of 300 mg. per kg. could be depended on to produce an extensive lesion of the islets of the pancreas with characteristic symptoms, many reports concerning alloxan diabetes in the laboratory animal appeared in the literature (1, 2, 3, 4, 7, 13, 19).

Those investigators have dealt with the production of alloxan diabetes in the adult animal, and, so far as we have been able to determine, no studies of the susceptibility of very young animals to alloxan have been heretofore carried out. Friedgood and Miller (10) found that the fetal rat is not susceptible to alloxan. The question arises, therefore, at what period of life does the animal become susceptible to alloxan?

METHOD

The young rabbits in our experiments were obtained from adults of mixed stock bred in the laboratory. In the adult rabbit it has been demonstrated that a 200 mg. per kg. dosage of alloxan produces a permanent diabetic state (1, 6). In this series, a dosage of 300 mg. per kg. was employed before the thirtieth day after birth; on the thirtieth dav and thereafter a dose of 200 mg. per kg. was employed. Thus, the young animals were given a dosage 50% greater than that which produces diabetes in the adult.

No animal was starved prior to injection. Intracardiac injections of alloxan were performed with a tuberculin syringe. Although the injection was rapid, blood was drawn into the syringe at the beginning, during the course of, and at the end of injection in order to confirm the intracardiac route. (Leech and Bailey have found that alloxan disappears almost completely from the blood within two minutes (21).)

The diabetic state of the animal was determined by the blood sugar level, the blood being withdrawn from the animal by intracardiac puncture. This procedure was employed until the veins of the ear were of adequate size. The Folin-Malmros microtechnique (9) was employed to determine the blood sugar values. In this series, animals with blood sugar levels exceeding 300 mg. per 100 ml. were considered to be diabetic (13). In no instance were the animals intentionally starved prior to a blood sugar determination. The frequent and prolonged absence from the mother which this procedure would entail, and the delicate nutritional status of the newborn rabbit, rendered fasting impracticable. From the majority of litters employed in this experiment one or two animals were selected as controls, blood sugar values being determined concurrently with those of the injected animals. These blood sugar values served as normal values and as controls over the blood sugar technique.

RESULTS

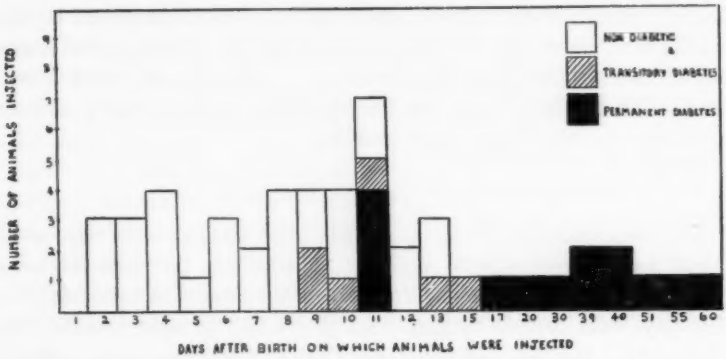
Fifty-one animals varying in age from two through sixty days after birth were injected with alloxan. Thereafter, the animals were weighed and blood sugar determinations were made at intervals of a few days over periods ranging from two weeks to eight months (see Table IA). Weights and blood sugar levels of ten litter mate controls are to be found in Table IB.

The distribution of diabetic animals in the total number injected is shown in Graph I. From this graph it will be noted that in none of the twenty animals injected prior to the ninth day were we able to demonstrate a diabetic state. Of the twenty-one animals injected from the ninth through the fifteenth day, four developed a permanent diabetes, six developed a transitory diabetes, and eleven failed to become diabetic. All of the ten animals injected after the sixteenth day of life developed a permanent diabetes.

This transitory alloxan diabetes in the laboratory animal, which we noted in six instances, has been reported in the literature (5, 6, 19, 21). We have classified an animal as a transitory diabetic provided that at least once following injection he is hyperglycemic to the extent of 300 mg. per 100 ml. We consider an animal to have a permanent

diabetes if the hyperglycemia is maintained. One animal (76-A3) has remained hyperglycemic over a period of one year. The remainder were either sacrificed or died during the course of their diabetes.

Statistical analysis of these data indicates the significance of the failure to produce demonstrable diabetes in the twenty animals injected prior to the ninth day. The expected incidence of diabetes in these animals would be 64.5%, this being the incidence of diabetes in the group injected on the ninth day and following. The standard error of the difference between the two groups is 8.6. The experimental


NUMBER OF ANIMALS INJECTED
NON DIABETIC
&
TRANSITORY DIABETES
PERMANENT DIABETES
1 2 3 4 5 6 7 8 9 10 11 12 13 15 17 20 30 39 40 51 55 60
DAYS AFTER BIRTH ON WHICH ANIMALS WERE INJECTED

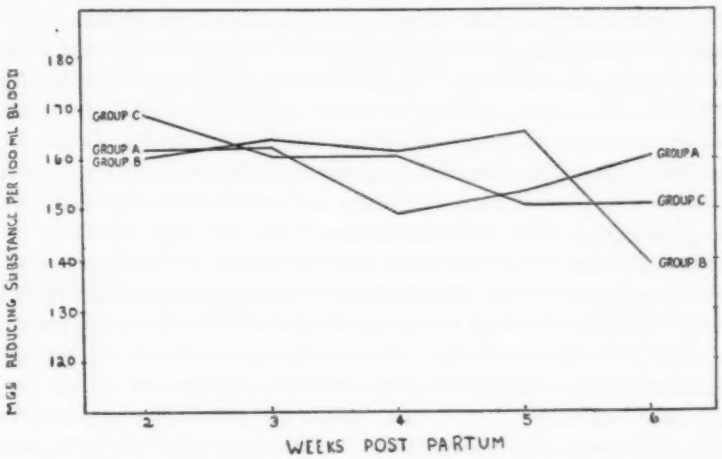
GRAPH I. Age distribution of animals injected with alloxan per day post partum and the incidence of diabetes.

incidence in the younger group was 0.0%, or exactly 7.5 standard errors from the incidence in the older group, 64.5%.

The blood sugar determinations were compiled and studied in the following manner. First, it was decided to determine the blood sugar levels in the normal, non-fasting, nursing animal. Blood sugar values were determined on each of twenty-eight animals several times every week from the second through the sixth week after birth. The values for all animals during each week were grouped, and an average value computed (Group A). The non-diabetic injected animals in the series were divided into two groups. Group B comprises all animals injected prior to the ninth day after birth. Group C includes those animals injected on the ninth day or after which failed to develop a

demonstrable diabetes. An average weekly value for each group was calculated by the method employed for Group A. The average blood sugar levels of each separate group are compared in Graph II. Statistical studies indicate that the blood sugar levels of Groups B and C do not deviate significantly from the blood sugar levels of Group A during corresponding weekly intervals.

In Table IA it will be noted that several relatively high blood sugar values were found in animals which have not been considered diabetic. When these values were obtained, control litter mates had similar



GRAPH II. Average weekly blood sugar levels of nondiabetic animals.

blood sugar levels (see Table IB). It was noted in general that the average blood sugar levels of the young, nursing animals were higher than the average blood sugar levels of the adult animal.

Duffy (6) noted that the appearance of diabetes was correlated with a loss of weight. This is indicated in our series: 76-A3, 98-1 (reinjection), 98-2 (reinjection), 105-1, 105-2, 105-3, and 105-A9 showed a definite loss of weight at various periods after injection; 57-1, 76-A2, and 71-A2 did not show this relationship; while the correlation in 75-1 and 76-A5 is questionable. This relationship between weight and the diabetic state is demonstrated in Table IA.

One observes in Table IA that the period required for the development of a demonstrable diabetes varies greatly. On the first blood sugar determination following injection thirteen animals were diabetic within the first three days. This includes one animal which died in hypoglycemic convulsions. One animal was found diabetic on the fifth day, the first analysis following injection. Four other animals were found diabetic between the seventh and twelfth days following injection. Another animal was found to be diabetic on the fifteenth day after injection. In one animal, 76-A3, we are unable to determine the time of the appearance of the diabetic state. During the first two weeks after injection diabetes could not be demonstrated. Due to the vacation period no analyses could be made on this animal until five months after injection. At this time the animal was found to be diabetic. A number of investigators (2, 11) has reported that typical diabetes mellitus in the adult animal will develop during a short interval (24–36 hours) after injection of a diabetogenic dose of alloxan. However, Leech and Bailey (21) have indicated that the diabetic state may not appear until the first or second week following injection.

The question arose as to whether alloxan diabetes could be produced at a later period in those animals which had failed to develop diabetes when initially injected in the neonatal period. For this purpose four of those animals were chosen: 60-1 was injected with 200 mg. per kg. of alloxan two hundred days after the initial injection of 300 mg. per kg. on the sixth day after birth. The pre-injection blood sugar level was 122 mg. per 100 ml. of blood. A blood sugar level of 59 mg. per 100 ml. was obtained sixteen hours after the injection. Twenty-two hours after injection the animal died in hypoglycemic convulsions. 98-1 and 98-2 were injected with 200 mg. per kg. of alloxan thirty-one days after the original injection of 300 mg. per kg. of alloxan on the eighth day after birth. The pre-injection blood sugar level of 98-1 was 147; and that of 98-2 was 105 mg. per 100 ml. On the day following injection blood sugar levels of over 400 mg. per 100 ml. were obtained in both animals. And on three other occasions during the week following injection the blood sugar levels exceeded 400 mg. per 100 ml. These animals were maintained on insulin for eight days, and then sacrificed. 101-3 was injected with 200 mg. per kg. of alloxan fifty-one days following the initial injection of 300 mg. per kg. on the

ninth day after birth. The pre-injection blood sugar level was 109 mg. per 100 ml. Twenty-four hours later a blood sugar level of 43 mg. per 100 ml. was obtained, and within an hour the animal died in hypoglycemic convulsions. Thus, at these later injection dates all four animals demonstrated the usual reaction to alloxan.

HISTOLOGY

In this study Hematoxylin-eosin stains were employed routinely. On all pertinent material the *alpha* and *beta* cells of the islands were differentiated by Gomori's modification of his Chromium-hematoxylin-phloxin stain (12).

In order to evaluate the changes found in the pancreas of the young rabbit following the injection of alloxan, alloxan diabetes was produced in an adult animal, and the pancreas from this animal was studied, the animal having succumbed twenty-four hours following injection. Microscopically, aberrations from the normal similar to those described by other investigators (2, 7, 11) were found in the pancreas of this animal (see Fig. 1). The islands showed by both techniques, in varying degrees of severity, the following changes: loss of cording of the cells, loss of cellular outline, coalescense of the cytoplasm into an almost homogeneous debris, pyknosis, and a fading of the nuclei associated with a diminution in the affinity for the basic stain. In the majority of the affected islands were found several cells, apparently undisturbed, which the Gomori stain showed to be *alpha* cells; *i.e.*, the cytoplasm of the *alpha* cells stained a cherry red in contrast to the pale pink cytoplasm of the affected *beta* cells.

Changes in the pancreas of the young rabbits which developed diabetes were comparable to those in the adult rabbit described above (see Figs. 6, 7). In those injected animals in which a diabetic state was not demonstrated there were observed none of the characteristic changes in the pancreas (see Figs. 3, 4, 5). It is known that the *alpha* cells in general are not susceptible to the effects of alloxan (2, 5, 13), which led to the consideration that possibly the islands in these young unsusceptible animals consisted primarily of *alpha* cells. However, when differential stains had been carried out it was found that the majority of the cells in the pancreas of the neonatal rabbit are *beta* cells, and that *alpha* cells are rarely seen.

TABLE IA

Blood Sugar Levels And Weights Of Young Rabbits Injected With Alloxan

DAY AFTER BIRTH ANIMAL WAS INJECTED	ANIMAL NUMBER		TIME AFTER INJECTION																						
			Days														Weeks				Months				
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	3	4	5	6	3	5	6	7	8
2	74-1	B.S.	165						183							147	147	139					185	119	
		Wt.	80						147							230	310	475					3790	4015	
	74-2	B.S.	121						196							141	151	148					112	121	
		Wt.	62						90							149	220	315					2560	2705	
	74-3	B.S.	124						178							154	143	141					135		
		Wt.	60						95							156	225	360					3280		
3	74-5	B.S.	137	127				172							166		155	158							
		Wt.	58	64				121							189		270	410							
	104-2	B.S.		122					159		175	164				185	185	158							
		Wt.		93	98	123			143		179	207		260		311	490	670							
	105-A1	B.S.	106	117	115		167			123				148			189								
		Wt.	54	62	59		67			93				128			208								
4	86-2	B.S.						180						174			152						175		127
		Wt.						181						265			430						3540		3510
	104-4	B.S.	114					136		173	136				157	173	165								
		Wt.	104	104	115	120		130		143	156		180		228	412	635								
	105-A4	B.S.	90	125		109				148			168				174								
		Wt.	51	58		76				89			104				216								
	105-A5	B.S.	106	133		152				154			178				157								
		Wt.	67	71		82				112			118				233								
5	86-3	B.S.					172					149					139						112	120	
		Wt.					167					270					440						3810	3820	

		Wt.	67	71		82				112			118				233											
5	86-3	B.S.					172						149				139						112	120				
		Wt.					167						270				440						3810	3820				
6	58-1	B.S.					173					133					163	163										
		Wt.					218					360					510	720										
	58-2	B.S.					214					166					183	141										
		Wt.					203					320					475	650										
	60-1	B.S.					133						149				152						122					
		Wt.					162						270				410						4300					
7	101-B2	B.S.	139	168	151	167				165							156	163										
		Wt.	170	203	216	255				365							440	480										
	105-A7	B.S.	147	155		120				144				185			139											
		Wt.	100	110		132				159				197			325											
8	98-1	B.S.							95				248			173	169	216	147									
		Wt.							260				330			380	470	700	900									
	98-2	B.S.							170				188			220	230	135	105									
		Wt.							270				340			405	510	730	940									
	101-1	B.S.							215								197	156	158	130	107	102						
		Wt.							183				260		310		355	420	775	900	1190	2575						
	101-2	B.S.							207								201	121	168	107	109	103						
		Wt.							165				240		290		330	410	790	925	1420	2725						
9	75-1	B.S.							118				396*			145	66	140	147		174		148					
		Wt.							210				330			350	470	620	825		1060		3720					
	75-2	B.S.							124				193			225	161	130	167				155					
		Wt.							210				300			340	460	705	900				4020					

B.S. = Blood Sugar; Wt. = Weight;* = Insulin Administered.

TABLE IA—*Continued*

Blood Sugar Levels And Weights Of Young Rabbits Injected With Alloxan

DAY AFTER BIRTH ANIMAL WAS INJECTED	ANIMAL NUMBER		TIME AFTER INJECTION																						
			Days														Weeks				Months				
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	3	4	5	6	3	5	6	7	8
9	101-3	B.S.						198								195	159		166	137	109				
		Wt.						199				280		315		360	430	520	790	965	1540				
	105-2	B.S.					308		350*			136				160	167	200	167	152	178				
		Wt.					194	205	205	210	214	230				298	416	650	770	850	1025				
10	76-A1	B.S.			150		150		184			148				137						124			
		Wt.			162	179	185	192	220			225			275							3600			
	76-A2	B.S.			152		172		325			135				145						135		114	
		Wt.			157	170	178	184	215			250			285							3370		3545	
	86-5	B.S.		155						165							128						125		
		Wt.		156						260							385						3410		
	86-6	B.S.		180						153							124						120		
		Wt.		220						340							470						3960		
11	57-1	B.S.					174				296			381		226	182	150							
		Wt.					390				560			670		710	960	1240							
	58-3	B.S.		800*	dead																				
		Wt.		154																					
	58-4	B.S.		349	dead																				
		Wt.		165																					
	76-A3	B.S.		114	77	142		160			139				130							315	640*	475	381
		Wt.		160	155	148	141	156			185			220								2780	3040	3250	3410
	76-A4	B.S.		152		130		168			128				154							121			
		Wt.		170	193	207	198	230			235			275								3420			

	76-A4	B.S.		152		130		168			128				154													
		Wt.		170	193	207	198	230			235			275										121				
																								3420				
11	76-A5	B.S.		315*		450*		275			367*				295			dead										
		Wt.		156	165	174	184	210			215			250														
	76-A7	B.S.		153		165		149			121				130			sacrificed										
		Wt.		127	146	152	159	174			190			225														
12	76-A8	B.S.	157		157		168			184				151			sacrificed											
		Wt.	193	225	240	225	245			255			280															
	76-A9	B.S.	163	250	203		185			132														174				
		Wt.	102	97	113	122	142			180			240											3730				
13	59-1	B.S.	158		112				184		178					152	159											
		Wt.	270		305				450	510	525	545	590			660	750											
	71-A2	B.S.	288				340			164				175			166	145							55	113		
		Wt.	270				360			425				540			690	890							2580	2525		
	77-1	B.S.	170		176		168			197				203										145				
		Wt.	220	255	290	300	330			375			475											3590				
15	105-3	B.S.	162	265		186				175						160	313	312	185	203								
		Wt.	245	215	198	227				300						454	700	725	930	1225								
17	105-A9	B.S.	173		815	dead																						
		Wt.	209		180																							
20	107-2	B.S.	250	dead																								
		Wt.	323																									

B.S. = Blood Sugar; Wt. = Weight;* = Insulin Administered

TABLE IA—*Continued*

Blood Sugar Levels And Weights Of Young Rabbits Injected With Alloxan

DAY AFTER BIRTH ANIMAL WAS INJECTED	ANIMAL NUMBER		TIME AFTER INJECTION																				
			Days														Weeks				Months		
			1	2	3	4	5	9	7	8	9	10	11	12	13	14	3	4	5	6	3	5	6	7	8
30	79-3	B.S.	570	dead																					
		Wt.	425																						
39	83-1	B.S.			439*		82	sacrificed																	
		Wt.			720		750																		
	83-3	B.S.			135		175							332*			267*	344*	380*	320*	418*	sacrificed			
		Wt.			600		685							990			1090	1300	1490	1625	1800				
40	98-1	B.S.	462*		409*		431*		430	sacrificed															
		Wt.	840		760	795	810	855	855																
	98-2	B.S.	437*		435*		475*		400	sacrificed															
		Wt.	920		885	915	900	980	1015																
51	83-4	B.S.			405*	433*	dead																		
		Wt.	820		860	880																			
55	105-1	B.S.	411		504		dead																		
		Wt.	980		975																				
60	101-3	B.S.	43	dead																					
		Wt.	1570																						

B.S. = Blood Sugar; Wt. = Weight; * = Insulin Administered.

It was noted that within the first two to three weeks after birth the islands appear to be fewer in number than in older animals, and that for a month after birth the islands were of a smaller size in general than in older animals (see Figs. 2, 8). It is interesting to observe that Hughes and Hughes (16) found that in the rat the smaller the islet

TABLE IB

Blood Sugar Levels And Weights Of Control Non-Injected Young Rabbits

ANIMAL NUMBER		TIME AFTER BIRTH																
		Days													Weeks			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	3	4	5	6
58-5	B.S.			116		143				145						129	155		137
	Wt.			67		88				134						310	445		980
60-4	B.S.						138		144			111				169	154		174
	Wt.						92		117			168				265	405		870
71-A1	B.S.	85		66					126				190			190	184	125	145
	Wt.	38		40					180				320			400	510	710	1020
74-7	B.S.		117	129						166		225			191		129	151	
	Wt.		36	45						129		154			173		225	320	
74-8	B.S.		116	134						186		193			154		164	126	
	Wt.		34	44						109		141			162		225	380	
75-3	B.S.		106					153			95			158		175	142	141	123
	Wt.		45				108	131			210			310		340	470	660	840
76-A10	B.S.									166			131	162	125	158	138		
	Wt.									172			225	260	275	355	465		
98-3	B.S.		94					146				105			200	198	189	179	141
	Wt.		40					155				310			380	460	530	765	950
101-4	B.S.	103	142						110						100	185	207		181
	Wt.	46	54						109						185	315	490		960
105-A3	B.S.		108	116			120		164							126	177		
	Wt.		42	50			115		170							360	505		

B.S. = Blood Sugar; Wt. = Weight.

the larger the mean diameter of the *beta* cells, and that when alloxan was administered in repeated small doses it was the larger *beta* cells that were spared.

DISCUSSION

The results of this experiment indicate that with a dosage of alloxan even larger than that which regularly produced diabetes in the adult

rabbit a demonstrable diabetic state cannot be produced in the young rabbit prior to nine days after birth. Friedgood and Miller, who studied the response of the fetal rat to alloxan, drew the following conclusions: "1) In pregnant rats intravenously injected alloxan passes through the placenta into the fetal circulation within one or two minutes. 2) It does not, however, produce a permanent diabetes in the offspring. 3) The blood sugar values of the fetus parallel at a lower level that of the diabetic mother until parturition" (10). Our results indicate that a refractory state to alloxan exists in the rabbit following birth, and continues thereafter until at least nine days after parturition.

Before discussing possible reasons for this refractory state in the young rabbit, it is interesting to note that several factors have been reported in the literature which influence the production of diabetes by alloxan in the adult animal. Kass and Waisbren (18) have reported that fed rats are less susceptible to the diabetogenic action of alloxan than are those animals which have been starved for forty-eight hours prior to injection, the incidence of hyperglycemia being but 25% in animals whose food had not been withheld in contrast to an incidence of 92% in fasting animals. The same observers also noted, with no explanation, that epinephrine administered immediately before alloxan protected the fasting animals against the diabetogenic action of the drug. Attention has been centered on the rapid destruction of alloxan in the adult animal (14, 21). The present supposition is that the disappearance of alloxan from the blood stream is due to its combination with sulfhydryl compounds. Some evidence for this belief is contained in Leech and Bailey's observation that in rabbits the reduced glutathione of the blood disappeared coincidentally and parallel with the disappearance of injected alloxan (21). Lazarow (20) reported that the intravenous injection of large doses of glutathione or cysteine one to two minutes prior to the injection of a diabetogenic dose of alloxan completely protected rats from diabetes; and that when the sulfhydryl compounds were given one minute after the alloxan injection partial protection occurred, whereas when three or more minutes had elapsed there was no protection.

The explanation of the refractory state of the young rabbit is not evident at present. Two possibilities come to mind. First, the islet

cells of the pancreas at this period of life may be refractory to the drug. Second, alloxan may be destroyed or inactivated in the body immediately after the injection during this period. The evidence mentioned above leads one to consider the possibility that a greater concentration of sulfhydryl compounds may be present in the blood stream or pancreatic islet cells of the young animal than in the adult. In regard to this Needham states that the younger the animal the more glutathione it contains relatively (22). Thompson and Voegtlin found that the concentration of glutathione in the entire rat declines with age both during the embryonic and post-embryonic periods, but that the relationship was not necessarily true for each individual organ (24). In the rabbit this finding was confirmed by Santavy (23). However, the pancreas was not included in these reports.

TABLE II

Susceptibility To Alloxan Of Various Mammalian Species Compared With The Blood Cell Concentration Of Glutathione

SPECIES	MGS. GLUTATHIONE PER 100 GRAMS BLOOD CELLS	MGS. OF ALLOXAN PER KG. OF BODY WEIGHT
Rat	53	40 I.V.
Dog	79	50–100 I.V.
Rabbit	114	100–200 I.V.
Guinea pig	151	?*

I.V. = Intravenous.

* See text for explanation.

Goss and Gregory (15) demonstrated in newborn rabbits that sulfhydryl concentration of the entire body is related to nursing. Young which had nursed for forty-eight hours had a mean glutathione concentration of 63 mg. per 100 grams of body weight, while litter mates of the same age which had not nursed had a mean concentration of only 33.94 mg. of glutathione per 100 grams of body weight. Too, these authors found that the glutathione concentration in the newborn varied directly with the adult size of his race; and that the larger embryos within a race have at birth more glutathione than the smaller ones, and this is more the case in races of larger adult size than in those of smaller adult size.

We have collected data relative to the difference in the susceptibility to alloxan of various mammalian species in comparison with the blood

cell concentration of glutathione (Table II). It is interesting to note that the higher the average species blood cell concentration of glutathione, the greater the species resistance to the diabetogenic action of alloxan. The glutathione determinations are from the work of Thompson and Voegtlin (24). The usually efficacious dosages of alloxan for the dog and rabbit are from Goldner (11). The dosage for the rat is from Lazarow (20). Goldner (11) states that the exact dosage for the guinea pig has not been determined, since only a dosage which results in the death of the animal within twenty-four hours produces pancreatic lesions.

That resistance or susceptibility to the diabetogenic action of alloxan does not bear a simple relation to the amount of glutathione in the blood is indicated by the fact that Santavy (23) found that the glutathione content of the blood of the newborn rabbit is approximately one-half that of the adult, and yet our studies show a greater resistance in the newborn rabbit.

Our observations demonstrate that in each case a second injection of alloxan at a later date produced the characteristic response to the drug in animals refractory in the neonatal period. Other observers (5, 16, 19) have reported that in adult animals an animal that has proved refractory to a first dose of alloxan seldom responds to subsequent doses.

CONCLUSIONS

1) A dosage of 300 mg. per kg. of alloxan, which produces diabetes in the adult rabbit, failed to cause diabetes in rabbits when injected before the ninth day of life.

2) In four animals, which did not develop diabetes when injected in the neonatal period with 300 mg. per kg. of alloxan, a later injection of 200 mg. per kg. of alloxan, when the animals were one to six and one-half months old, did produce diabetes in each case.

Acknowledgements: We are deeply indebted to Dr. Peggy Ann Hanson, whose initial studies of the effects of alloxan in the pregnant animal (unpublished) stimulated our interest in this problem.

We wish to express our sincere appreciation to Dr. Arnold R. Rich for his encouragement and invaluable criticism throughout the course of this work.

REFERENCES

(1) Bailey, C. C. and Bailey, O. T. "Production of Diabetes Mellitus in Rabbits with Alloxan." *J. A. M. A.* **122,** 1165, 1943.

(2) Bailey, O. T., Bailey, C. C., and Hagan, W. H. "Alloxan Diabetes in Rabbits: Consideration of Morphological and Physiological Changes." *Am. J. M. Sc.*, **208,** 450, 1944.

(3) Brunschwigh, A., Allen, J. G., Goldner, M. G., and Gomori, G. "Alloxan." *J. A. M. A.* **122,** 966, 1943.

(4) Carrasco-Formiguera, R. "Alloxan Diabetes in Dogs." *J. Lab. & Clin. Med.* **29,** 510–517, 1944.

(5) Duff, G. L. "The Pathology of the Pancreas in Experimental Diabetes Mellitus." *Am. J. M. Sc.* **210,** 381–397, 1945.

(6) Duffy, E. "Alloxan Diabetes in the Rabbit." *J. Path. & Bact.* **57,** 143–149, 1944.

(7) Dunn, J. S., Kirkpatrick, J., McLetchie, N. G. B., and Telfer, S. V. "Necrosis of Islets of Langerhans Produced Experimentally." *J. Path. & Bact.* **55,** 245–257, 1943.

(8) Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B. "Necrosis of Islets of Langerhans Produced Experimentally." *Lancet* **1,** 484–487, 1943.

(9) Folin, O. and Malmros, H. "Blood Sugar and Fermentable Blood Sugar as Determined by Different Methods." *J. Biol. Chem.* **83,** 115, 1929.

(10) Friedgood, C. E. and Miller, A. A. "Alloxan in Pregnant Rats." *Proc. Soc. Exper. Biol. & Med.* **59,** 61–63, 1945.

(11) Goldner, M. G. "Alloxan Diabetes: Its Production and Mechanism." *Bull. N. Y. Acad. Med.* **21,** 44, 1945.

(12) Gomori, G. "Observations with Differential Stains on Human Islets of Langerhans." *Am. J. of Path.* **17,** 395, 1941.

(13) Gomori, G. and Goldner, M. G. "Production of Diabetes Mellitus in Rats with Alloxan." *Proc. Soc. Exper. Biol. & Med.* **54,** 287–290, 1943.

(14) Gomori, G. and Goldner, M. G. "Acute Nature of Alloxan Damage." *Proc. Soc. Exper. Biol. & Med.* **58,** 232, 1945.

(15) Gregory, P. W. and Goss, H. "Glutathione Concentration and Hereditary Body Size." *J. Exper. Zool.*, **66,** 155, 1933.

(16) Hard, W. L. and Carr, C. J. "Experimental Diabetes Produced by Alloxan." *Proc. Soc. Exper. Biol. & Med.*, **55,** 214–216, 1944.

(17) Hughes, H. and Hughes, G. E. "The Effect of Prolonged Administration of Alloxan upon the Islet Tissue of the Rat Pancreas." *Brit. J. Exper. Path.* **25,** 126–131, 1944.

(18) Kass, E. H. and Waisbren, B. A. "A Method for Consistent Induction of Chronic Hyperglycemia with Alloxan." *Proc. Soc. Exper. Biol. & Med.* **60,** 303–306, 1945.

(19) Kenedy, W. B. and Lukens, D. W. "Observations on Alloxan Diabetes." *Proc. Soc. Exper. Biol. & Med.* **57,** 143–149, 1944.

(20) Lazarow, A. "Protective Effect of Glutathione and Cysteine Against

Alloxan Diabetes in the Rat." *Proc. Soc. Exper. Biol. & Med.* **61,** 441–447, 1946.

(21) LEECH, R. S. AND BAILEY, C. C. "Blood Alloxan and Blood Glutathione in Rabbits Injected with Alloxan." *J. Biol. Chem.* **157,** 525–542, 1945.

(22) NEEDHAM, J. "Biochemistry and Morphogenesis." *The University Press.* Cambridge, Eng., 1942.

(23) SANTAVY, F. "Les Variations des Taux de Glutathione chez les Animaux Nouveau-Nes." *J. de Phys. et de Path. G.* **36,** 1089–1097, 1938.

(24) THOMPSON, J. AND VOEGTLIN, C. "Glutathione Content of Normal Animals." *J. Biol. Chem.* **70,** 733, 1926.

DESCRIPTION OF FIGURES

(Photomicrographs by Miss Marjorie Jackson.)

All photomicrographs were taken with blue and yellow filters at the same magnification. The islands illustrated are in each case characteristic of those seen in the respective sections.

FIG. 1. Necrotic island of Langerhans of adult rabbit 69 twenty-four hours after injection with 200 mg. per kg. of alloxan. Hematoxylin-eosin stain.

FIG. 2. Island of Langerhans of normal rabbit 72–4, killed five days after birth. Chromium-hematoxylin-phloxin stain.

FIG. 3. Island of Langerhans of rabbit 105-A3, injected with 300 mg. per kg. of alloxan on the fourth day after birth and killed on the twelfth day after birth. No hyperglycemia; no histological changes typical of alloxan damage. Hematoxylin-eosin stain.

FIG. 4. Island of Langerhans of rabbit 105-A5, injected with 300 mg. per kg. of alloxan on the fourth day after birth and killed on the thirty-second day after birth. No hyperglycemia; no histological changes typical of alloxan damage. Chromium-hematoxylin-phloxin stain.

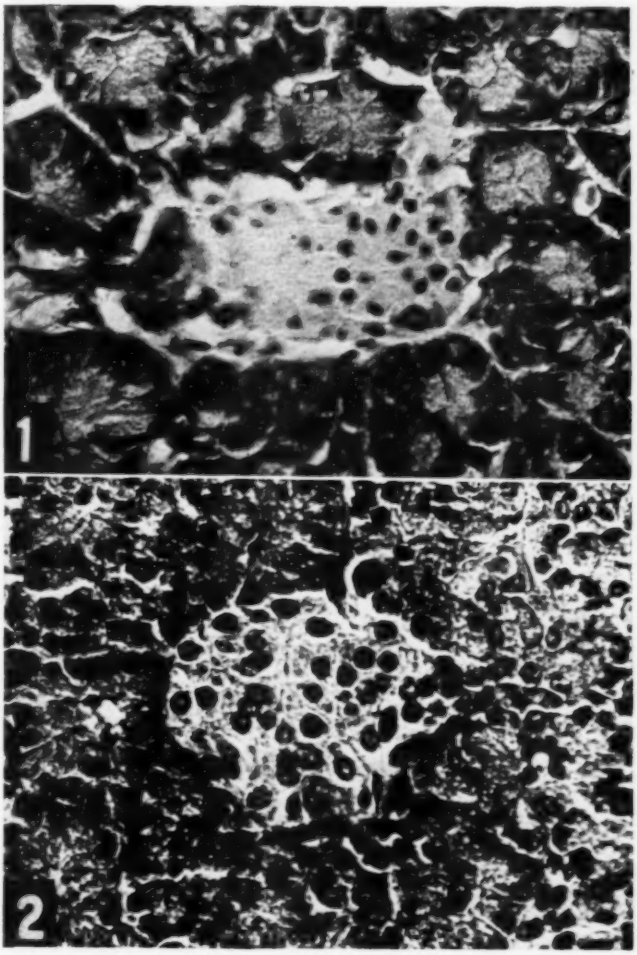
FIG. 5. Island of Langerhans of rabbit 101-B2, injected with 300 mg. per kg. of alloxan on the seventh day after birth and killed on the thirtieth day after birth. No hyperglycemia; no histological changes typical of alloxan damage. Hematoxylin-eosin stain.

FIG. 6. Necrotic island of Langerhans of rabbit 76-A6, injected with 300 mg. per kg. of alloxan on the eleventh day after birth and dead on the following day. No blood sugar determination was made. Hematoxylin-eosin stain.

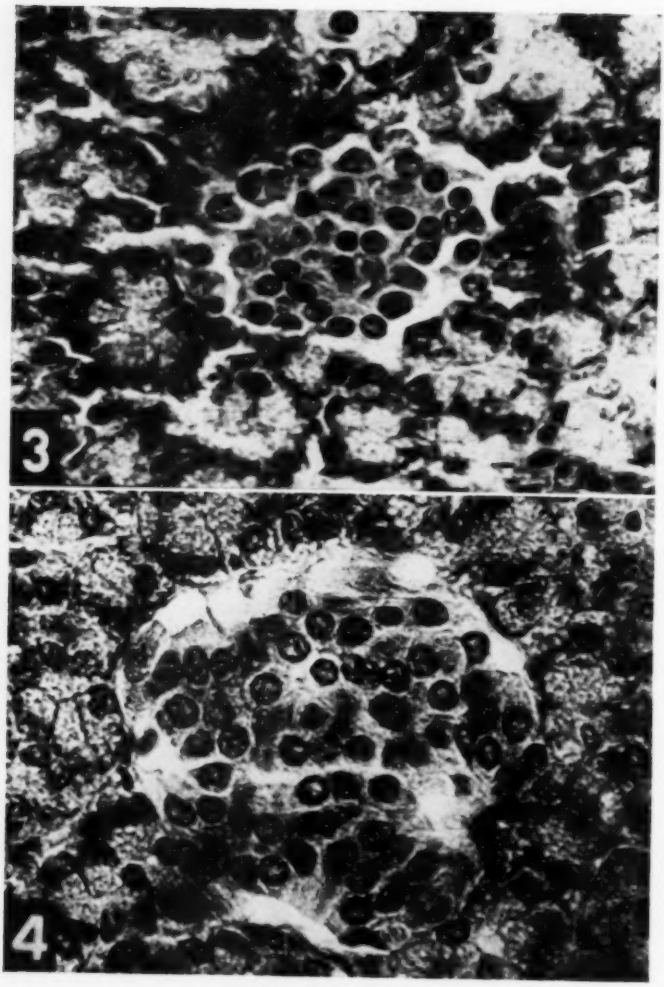
FIG. 7. Necrotic island of Langerhans of rabbit 105-A9, injected with 300 mg. per kg. of alloxan on the seventeenth day after birth and dead on the twentieth day after birth. Hyperglycemia. Hematoxylin-eosin stain.

FIG. 8. Island of Langerhans of normal rabbit 79-4, killed nineteen days after birth. Hematoxylin-eosin stain.

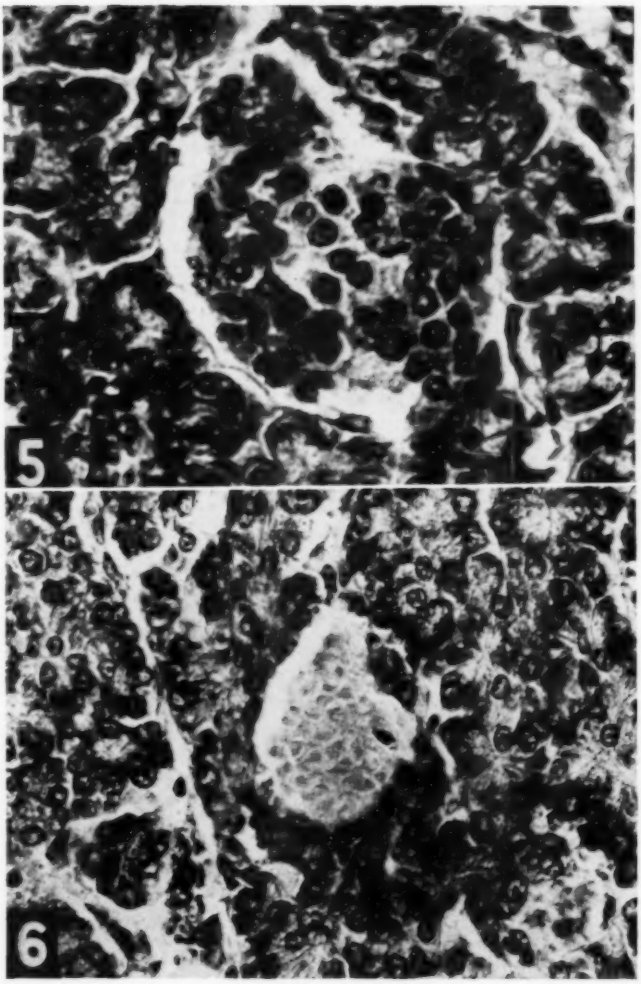
FIG. 9. Necrotic island of Langerhans of rabbit 60-1, first injected with 300 mg. per kg. of alloxan on the sixth day after birth. No hyperglycemia. Reinjected with 200 mg. per kg. of alloxan on the two hundredth day after birth. The animal died in hypoglycemic convulsions the following day. Hematoxylin-eosin stain.



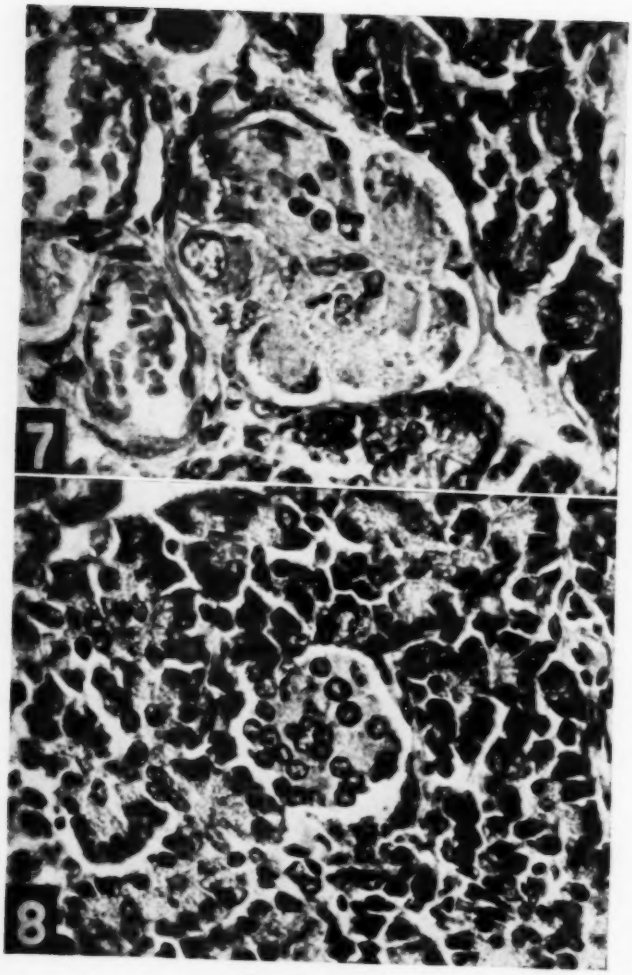
FIGS. 1 AND 2.



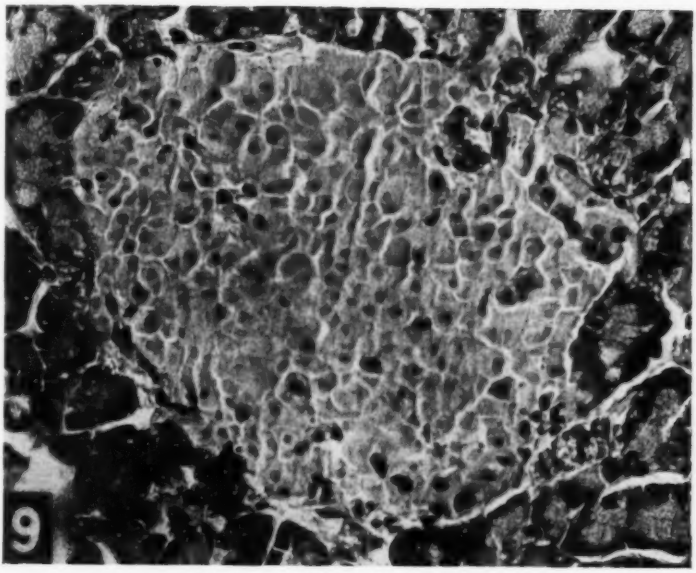
FIGS. 3 AND 4.



FIGS. 5 AND 6.



FIGS. 7 AND 8.



FIGS. 9.

MALIGNANT TUMORS OF THE NASOPHARYNX

THOMAS E. VAN METRE, JR.

From the Department of Medicine, The Johns Hopkins Hospital and School of Medicine

Received for Publication July 25, 1947

MALIGNANT TUMORS OF THE NASOPHARYNX

The purpose of this paper is to review the clinical characteristics of malignant tumors of the nasopharynx, as they were demonstrated in forty-six cases studied at the Johns Hopkins Hospital between 1925 and 1946.

Nasopharyngeal malignancies have attracted considerable interest because they produce such a perplexing array of local, neurological, otological, and cervical glandular manifestations. They have been studied by many workers, and there are many excellent articles on the subject. The literature has been adequately reviewed by Godtfriedson (1) in his comprehensive monograph reporting 453 new cases. The cases to be reported in this paper add nothing new to the wealth of material already published. But repetition is indicated for two reasons. First, these tumors still are misdiagnosed frequently. Second, they demonstrate points of fundamental value, inasmuch as the varied lesions produced can be explained by consideration of the properties of neoplastic growth, the anatomy of the nasopharynx, and the pathophysiological disturbances created by pressure, obstruction, and destruction.

Materials: Forty- six cases of malignant tumor of the nasopharynx studied at the Johns Hopkins Hospital between 1925 and 1946 have been analyzed. In all of the cases considered, a growth could be seen in the nasopharynx. In thirty-three cases, the clinical picture seemed sufficient to establish the diagnosis, even though microscopic evidence was lacking. All of these patients have been examined completely by many observers, all of them have had examination by ear, nose and throat consultants, many have had examination by neurological consultants. Only the data agreed on by all observers have been included. The material has been assembled in the tables that follow. Treat-

ment and mortality are not analyzed because of insufficient data. Godtfriedson covers these subjects adequately.

Results: In Table 1, I have gathered under pertinent headings the salient facts known about each case. Only such detailed analysis can bring out the many different combinations of signs and symptoms presented by the individual case. This compilation of data can be further analyzed as follows.

Types of Tumors: I have not attempted to differentiate minutely the types of tumors involved because the material at hand is inadequate for such study. Such precise work requires serially sectioned autopsy material rather than the small, frequently distorted biopsy material usually obtained. With the aid of the pathology department, the tumors have been divided into the types shown in Table 2. No attempt will be made to consider the relationship between clinical picture and tumor type because of inadequate number of cases for significant statistical study. Godtfriedson brings forth many interesting correlations between tumor type and frequency of various symptoms and signs, but admits that epithelial and mesothelial tumors are both capable of producing similar results.

Incidence: Malignant tumors of the nasopharynx occur at all ages, in negroes and white people, in males and females. Like most malignancies, these occur in highest incidence in the fifth to sixth decade (Table 3). Of these cases 63% occurred in males. For unexplained reasons, males have the disease more commonly than females.

Symptomatology and Signs: These fall into four main groups which may be classified as follows:

1. Nasopharynx: In all cases a visible growth was present. This growth made itself known in many cases by producing obstruction to breathing, discharge (frequently bloody), and pain.

2. Ear: Many cases had some or all of the symptoms and signs of tubal occlusion, including tinnitus, air conduction deafness, feeling of fullness in the ear, and retraction of the ear drums. Acute otitis media was present in one case.

3. Cervical glands: Enlarged cervical glands with signs of metastatic involvement were common. Sometimes these were present on one side, more often they were bilateral. The glands between the tip of the mastoid and the sternocleidomastoid muscle were most frequently involved.

TABLE 1

The clinical picture presented by 46 cases of malignant tumors of the nasopharynx.

CASE AND SERIAL NUMBER	COLOR	SEX	AGE	1ST SYMPTOM	INTERVAL 1ST SYMPTOM TO ADMISSION	CERVICAL GLANDS	NASOPHARYNX*	EAR	CRANIAL NERVES INVOLVED	X-RAY SKULL	REMOTE METASTASES	OTHER	TYPE TUMOR
1. 279520	W	M	32	Tinnitus & deafness leaf ear	2½ mos.	R and L	0	Right ear tinnitus AC deafness and drum retraction	R 6, 9, 10, 12	Clouding of right antrum and ethmoid; erosion of base of skull	0	Generalized headache	Squamous cell, carcinoma
2. 294492	C	M	20	Right sided headache	1 year	R	0	Right ear tinnitus & AC deafness	R 5, 6	Negative	None demonstrated	0	Carcinoma
3. U37287	W W	F	54	Nasal obstruction	1 year	0	Obstruction. Bloody discharge	Right ear feeling of fullness and drum retraction	0	Not obtained	None demonstrated	0	Carcinoma
4. U38410	W	M	68	Pain left side of face	3 mos.	R and L	0	Right ear tinnitus and AC deafness	L 5, 7, 9, 10, 12	Not obtained	None demonstrated	0	Carcinoma
5. U52262	W	M	21	Painful swelling left cervical node	15 mos.	L	0	Left ear AC deafness	L 5	Negative	None demonstrated	0	Squamous cell, carcinoma
6. U30884	W	M	30	Painful swelling right cervical node	4 mos.	R	Bloody discharge	Right ear AC deafness	R 5, 9, 10, 12	Negative	None demonstrated	0	Carcinoma
7. U23190	W	M	67	AC deafness right ear	3 years	0	0	Right ear AC deafness	R 3, 7, 9	Not obtained	None demonstrated	0	Carcinoma
8. U21715	W	F	58	Tinnitus and AC deafness left ear		0	0	Left ear tinnitus and AC deafness	L 5, 6, 9, 10	Not obtained	None demonstrated	Left sided headache; agraphia	Carcinoma
9. 180335	W	M	48	Postnasal drip and bloody sputum	5 mos.	R and L	Bloody sputum. Postnasal drip	Right ear AC deafness	R 5	Not obtained	None demonstrated	0	Carcinoma
10. 203047	W	M	42	Diplopia (R. 6 nerve)	1 mo.	R and L	0	Both ears AC deafness and retracted drums	L 2, 5, 6	Destruction R ethmoid, L. orbit and middle fossa	None demonstrated	Proptosis left eye	Squamous cell, carcinoma

11. 267595	W	M	48	Right occipital headache			Bloody discharge	Both ears AC deafness and feeling of fullness	R 5	Displacement of air column, clouding of ethmoid sinus, erosion of base of skill	None demonstrated	Herpes right forehead	Squamous cell, cincaroma
12. 272736	W	M	73	AC deafness left ear	2 years	L	0	Left ear AC deafness	0	Not obtained	None demonstrated	0	Squamous cell, carcinoma
13. U68690	W	M	51	Painless swelling of right cervical glands.	1 year	R and L	0	Right ear AC deafness	R 5	Not obtained	None demonstrated	0	Adenocarcinoma
14. U63824	C	M	48	Pain in lumbosacral region	6 mos.	R and L	Bloody discharge	Left ear AC deafness and drum retraction	0 0	Not obtained	Pelvis sacrum lumbar spine	0	Squamous cell, carcinoma
15. U59176	W	M	23	Painless swelling right cervical nodes	15 mos.	R and L	0	Right ear AC deafness and drum retraction	0	Not obtained	None demonstrated	0	Squamous cell, carcinoma
16. U58026	W	F	61	Pain right side of face	1 mo.	R and L	0	Right ear AC deafness and acute otitis media	0	Not obtained	None demonstrated	0	Squamous cell, carcinoma
17. U46550	C	F	44	Sore throat and base of tongue	11 mos.	R and L	0	0	0	Not obtained	None demonstrated	0	Squamous cell, carcinoma
18. U45682	C	M	35	AC deafness left ear	1 year	R and L	0	Left ear AC deafness	L 5, 10	Not obtained	Ribs	0	Carcinoma
19. U53076	C	M	35	Painless swelling right cervical nodes	1 year	R	Obstruction	Both ears AC deafness	R 5	Not obtained	None demonstrated	0	Squamous cell, carcinoma
20. 111853	W	M	47	Stiffness of jaw with difficulty in opening mouth	1 year	R and L	0	Left ear tinnitus and AC deafness	L 2, 5, 6 L sympathetic	Air column displaced destruction of base of skull	None demonstrated	0	Squamous cell, carcinoma
21. 148251	W	M	44	Tinnitus and AC deafness right ear	3½ years	0	Bloody discharge	Right ear tinnitus and AC deafness	R 2, 3, 5	Clouding of ethmoid destruction of right middle fossa	None demonstrated	0	Carcinoma
22. 148251	W	F	63	Nasal obstruction	2 years	R and L	Obstruction. Bloody discharge	Right ear AC deafness	0	Not obtained	None demonstrated	Frontal headache	Carcinoma

TABLE 1–*Continued*

CASE AND SERIAL NUMBER	COLOR	SEX	AGE	1ST SYMPTOM	INTERVAL 1ST SYMPTOM TO ADMISSION	CERVICAL GLANDS	NASO-PHARYNX*	EAR	CRANIAL NERVES INVOLVED	X-RAY SKULL	REMOTE METASTASES	OTHER	TYPE TUMOR
23. 391469	W	F	45	Postnasal drip	1½ years	R and L	Obstruction. Bloody discharge	Both ears tinnitus AC deafness and drum retraction	R and L 6, 10, 12,	Displacement of air column	None demonstrated	General headache, fits of weakness, feeling hot, defecating and urinating	Squamous cell, carcinoma
24. 331009	C	M	44	Pain left temple, ear and nose	1 year	0	0	Left ear AC deafness	0	Displacement of air column. Clouding of left antrum and sphenoid	None demonstrated	0	Squamous cell, carcinoma
25. 168735	C	M	57	Nasal obstruction	1 year	R and L	Obstruction. Bloody discharge	Left ear AC deafness and drum retraction	L 5, 7, 11	Displacement of air column. Destruction of base of skull.	None demonstrated	0	Squamous cell, carcinoma
26. U46131	C	M	52	Sore throat and swollen neck glands	4 mos.	R and L	Bloody discharge	Left ear AC deafness	0	None obtained	None demonstrated	0	Carcinoma
27. 324885	W	M	54	Obstruction left side of nose	8 mos.	R and L	Obstruction. Bloody discharge	0	0	Displacement of air column	None demonstrated	0	Lymphoepithelioma
28. A16216	W	M	4	Pain right side of face	6 wks.	R and L	Obstruction. Bloody discharge	Right ear AC deafness	R 3, 4, 5, 6	Displacement of air column erosion of nose bones	None demonstrated	Nystagmus. EEG showed irritative focus on right side	Rhabdomyoma
29. 164637	C	F	4	Sore throat	4 days	R and L	0	Left ear otitis media	L 5, 6, 7	Not obtained	Lung	0	Sarcoma

30. U5314	W	F	69	Pain right side of face	2 years	R and L	0	Right ear tinnitus AC deafness	R 1, 5, 7, 9	Negative	None demonstrated	0	Sarcoma
31. 191363	W	M	53	Tinnitus right ear	1 year	R and L	Obstruction. Bloody discharge	Right ear tinnitus AC deafness and drum retraction left ear drum retraction	0	Not obtained	Enlarged spleen, axillary and inguinal nodes	0	Lymphosarcoma
32. 142011	W	F	25	Low lumbar pain	1 year	R and L	Bloody discharge	Feeling of fullness in both ears	0	Not obtained	Abdominal mass, ascites, and hydrothorax	0	Lymphosarcoma
33. U2111	C	F	50	Painless swelling left cervical glands	4 mos.	R and L	Bloody discharge	Both ears tinnitus AC deafness and drum retraction	0	Not obtained	Retroperitoneal axillary and inguinal nodes	0	Round cell sarcoma
34. U73624	W	F	38	Tinnitus right ear	1 year	R and L	Postnasal drip that is often bloody	Right ear tinnitus AC deafness fluid level	R 5, 6, 7	Negative	None demonstrated	Vomiting	No biopsy
35. U72595	C	M	53	Generalized headache	3 years	R and L	Bloody discharge	0	0	Not obtained	None demonstrated	0	No biopsy
36. U64870	W	M	48	Pain left temporoparietal region	9 mos.	L	Bloody discharge	Left ear tinnitus and AC deafness	L 3, 5, 7	Not obtained	None demonstrated	0	No biopsy
37. U58297	C	M	51	Painless swelling of left cervical nodes	2 years	R and L	0	Left ear tinnitus AC deafness and drum retraction	L 5	Not obtained	None demonstrated	0	No biopsy
38. U46380	W	M	25	Pain right side neck, head, and face	14 wks.	R and L	0	Right ear tinnitus AC deafness and drum retraction	R 2, 5, 6, 7, 9, 10, 12	Not obtained	None demonstrated	Projectile vomiting	No biopsy
39. U51280	W	F	45	Painless swelling of right cervical nodes	2 years	R and L	Bloody discharge	Right ear tinnitus AC deafness and drum retraction	R 5, 9, 10	Not obtained	None demonstrated	0	No biopsy
40. U60527	C	F	18	Pain left side neck, head, and face	4 mos.	L	0	Both ears AC deafness	L 5, 6, 9, 10, 12	Not obtained	None demonstrated	Vertigo, staggers to right	No biopsy

TABLE 1–*Concluded*

CASE AND SERIAL NUMBER	COLOR	SEX	AGE	1ST SYMPTOM	INTERVAL 1ST SYMPTOM TO ADMISSION	CERVICAL GLANDS	NASOPHARYNX*	EAR	CRANIAL NERVES INVOLVED	X-RAY SKULL	REMOTE METASTASES	OTHER	TYPE TUMOR
41. U95596	W	F	62	Pain right temporal region	10 mos.	0	Bloody discharge	Right ear AC deafness and tinnitus	R 5, 9, L 8, 10	Destruction of floor of anterior fossa. Involvement of posterior ethmoid and sphenoid sinuses and of petrous bone.	None demonstrated	Vomiting	No biopsy
42. 122111	W	F	61	Pain right occipital facial region	14 mos.	R and L	Bloody discharge	Right ear AC deafness and drum retraction	R 5	Destruction of right sphenoid	None demonstrated	0	No biopsy
43. U24565	W	F	16	Nasal obstruction	1½ years	R and L	Non-bloody discharge	Both ears AC deafness and drum retraction. Left ear tinnitus	L 3, 4, 9 10	Not obtained	None demonstrated	Left suboccipital headache	No biopsy
44. 193073	W	F	38	Decreased vision right eye	1 year	0	Bloody discharge	Right ear tinnitus and AC deafness	R 2, 5, 6, 9, 10, 12	Destruction of right middle fossa	Bones of thorax and extremities. Lungs	Generalized headache worse in occipital region	No biopsy
45. U72431	W	M	53	Right ear AC deafness and feeling of fullness	3 mos.	0	0	Right ear AC deafness and drum retraction	0	Negative	None demonstrated	0	No biopsy
46. 295231	W	F	54	Right ear AC deafness	4 years	0	Bloody discharge	Right ear AC deafness	R 5, 6, 7, L 2	Destruction of middle fossa, right sphenoid sinus and right orbit	None demonstrated	Vomiting Proptosis right eye	No biopsy

* In every one of these forty-six cases a visible growth was present in the nasopharynx. Only findings other than visible growth are mentioned therefore in this column.

4. Neurological: Symptoms and signs of involvement of cranial nerves were frequently present. Pain and anaesthesia in appropriate

TABLE 2

The types of tumors found in the 46 cases of malignant tumor of the nasopharynx

Epithelial Tumors	
Squamous cell carcinoma	14
Carcinoma	11
Adenocarcinoma	1
Mesothelial Tumors	
Lymphosarcoma	3
Sarcoma	2
Rhabdomyoma	1
Lymphoepithelioma	1
Non Biopsied Tumors	13

TABLE 3

The age of the patients in 46 cases of nasopharyngeal malignancy

AGE	NUMBER OF CASES
1–10	2
10–20	3
20–30	5
30–40	5
40–50	12
50–60	11
60–70	7
70–80	1

TABLE 4

Classification of the type of first symptom in forty-six cases of malignancy of the nasopharynx

Nasopharynx	10 cases
Ear	10 cases
Cervical Gland	9 cases
Neurological	14 cases
Pain Lumbosacral Region	2 cases
Generalized Headache	1 case

distribution marked involvement of sensory nerves. Weakness, paralysis, and atrophy of appropriate muscles marked involvement of motor nerves.

The first symptom was in almost equal proportion referred to one of the four main groups (Table 4). Where the first symptom was neurological, in 85% of the cases it was fifth nerve pain. In two cases, pain from metastases in the lumbosacral region produced the first symptom. In one case generalized headache, probably on the basis of invasion of the base of the skull, was the first symptom.

TABLE 5

The interval between the first symptom and admission in 46 cases of nasopharyngeal malignancy

INTERVAL BETWEEN FIRST SYMPTOM AND ADMISSION	NUMBER OF CASES
0– 4 months	12
4– 8 months	3
8–12 months	17
1– 2 years	10
2– 3 years	2
3– 4 years	2

TABLE 6

The incidence of various types of symptoms and signs on admission in forty-six cases of malignancy of the nasopharynx

Nasopharynx (exclusive of visible growth which was present in all cases)	25 cases = 52%
Ear	43 cases = 93%
Cervical Gland	36 cases = 78%
Neurological	31 cases = 67%
Headache	5 cases = 11%
Vomiting	5 cases = 11%

The interval between the first symptom and admission to the hospital varied considerably, as may be seen in Table 5. In many of these cases, the delay in great part was due to misdiagnosis.

On admission to the hospital, the patients almost always had overt manifestations of their disease, falling into several of the main groups already discussed (Table 6). The neurological lesions were very varied (Table 7). Frequently, there were multiple lesions. The fifth nerve was the one most frequently involved. In one instance (case 20) a true Horner's syndrome was present. Headache, usually occipital, which did not seem to be related to cranial nerve involvement, was observed in five instances. Projectile vomiting was seen in five instances.

Special studies: Either the throat mirror or the nasopharyngoscope

was necessary for adequate visualization of the tumor. Roentgenograms of the skull were obtained in only twenty-one of the forty-six

TABLE 7

The distribution of neurological involvement in the cases after full development. 31 of the 46 cases had some manifestations of neurological involvement. Frequently, more than one nerve was affected in a single case.

CRANIAL NERVE INVOLVED	NUMBER OF CASES
I	1
II	6
III	6
IV	3
V	27
VI	13
VII	10
VIII	1
IX	13
X	11
XII	8
Cervical Sympathetic	1

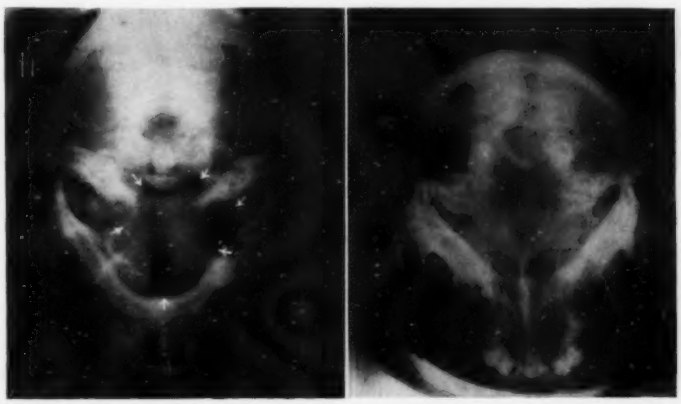


FIG. 1. Erosion of base of skull by carcinoma of nasopharynx. There is a huge defect in both the sphenoid bone and the clivus of the occipital bone. This defect has been outlined with arrows.

cases. They proved to be of considerable help diagnostically. Definite erosion of the base of the skull, of the type shown in Figure 1,

was demonstrated in twelve instances. The soft tissue shadow of the tumor displacing the nasopharyngeal air column, as in Figure 2, was demonstrated in seven instances. The roentgenograms showed no evidence of tumor in seven instances. Had anteroposterior and lateral films of the skull and stereoscopic films of the base of the skull been taken routinely in all cases, they probably would have revealed evidence of tumor in a large percentage of the cases.

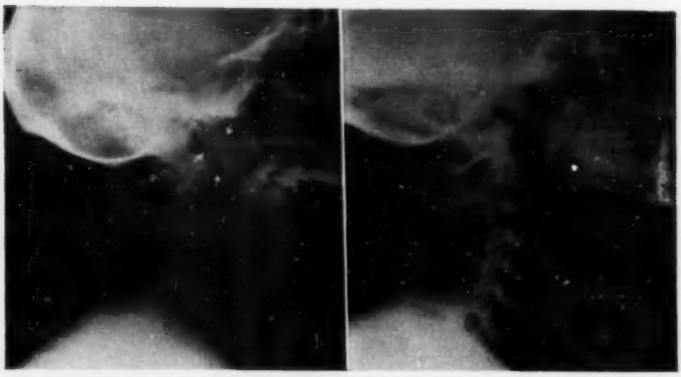


FIG. 2. Displacement of air column by carcinoma of nasopharynx. The wide air column which normally traverses the nasopharynx and can be seen overlying the superior rami of the mandible has been obliterated by a soft tissue mass which has been outlined by arrows.

Autopsy Examination: Seven of the forty-six cases were autopsied. In two autopsied cases, 12 and 33, the findings were an ulcerated tumor in the nasopharynx with metastases in cervical lymph nodes. In the first case, the tumor was a squamous cell carcinoma; in the second, a round cell sarcoma. The round cell sarcoma had also extended to retroperitoneal, axillary, and inguinal lymph nodes. In both of these cases, the autopsy findings confirmed the clinical impression. There were no neurological manifestations. There was no demonstrated invasion of the base of the skull.

Five autopsies were performed on cases with neurological manifestations. Unfortunately, in no case were the cranial nerves dissected out and special stains applied in order to determine the point of involve-

ment. However, in all cases, tumor infiltrated the bones at the base of the skull in areas where the nerves clinically involved might well have been affected. These data are summarized in Table 8.

Comment: The clinical picture presented by these tumors is explained by the following considerations.

The tumors are surface growing neoplasms, which tend to overgrow their blood supply and become necrotic. Secondary ulceration and infection frequently develop. A certain amount of hemorrhage, discharge, and local pain is therefore to be expected. Moreover, such a growth is a space occupying lesion capable of producing nasal obstruction when it becomes large enough.

These growths start in the neighborhood of the Eustachian tube orifices, and, by direct extension and the production of secondary edema, they readily occlude these orifices. Inadequate drainage of the middle ear results, and there follows the usual sequence to the blockade of any air filled space in the body—resorbtion of air, accumulation of secretions, and susceptibility to infection. Resorption of air from the middle ear produces tinnitus, causes a feeling of fullness in the ear, and leads to deafness. Accumulation of secretion causes the fluid level and bulging drum observed in case 34. Infection produces otitis media as in case 16.

The lymphatic drainage of the nasopharynx is rich and these tumors are very malignant. Early extension via lymphatics would be expected. The main drainage is to cervical nodes, those between the tip of the mastoid and the sternocleidomastoid muscle being the first major way stations. These nodes are usually the first to be involved.

The nasopharynx lies in close proximity to many cranial nerves. The cranial nerves emerge from the brain stem and penetrate the base of the skull which forms the roof of the nasopharynx. The roentgenogram and autopsy evidence indicate that the base of the skull is frequently invaded by the tumor. Such invasion is usually most extensive in the areas where the clinically involved nerves might be affected. The fact that the foramen lacerum and the Eustachian tube allow an easy gateway to the region of the petrous tip probably accounts for the high incidence of involvement of the fifth nerve and the nerves to the extra-ocular muscles. The cervical sympathetic supply to the eye may be interrupted either here or in the neck (by cervical metasta-

TABLE 8

Significant findings at autopsy in cases with neurological involvement

CASE	CLINICAL NEUROLOGICAL INVOLVEMENT	ROENTGENOGRAM OF SKULL	SIGNIFICANT AUTOPSY FINDINGS
8	L. 5,6,7,9,10	None taken	Carcinoma of the nasopharynx. The growth had invaded the petrous portion of the temporal bone, involving it completely. It had spread beneath the dura where involvement of the cranial nerves occurred. The left temporal lobe was penetrated along the VIII nerve.*
20	L. 2,5,6	Destruction of base of skull	Squamous cell carcinoma of the nasopharynx. Tumor was found invading the base of the skull. On the left lateral aspect of the sphenoid bone, the tumor had apparently completely invaded the dura and was growing along the inner surface about the cranial nerves, especially the fifth which was surrounded by tumor. Tumor had destroyed the bone beneath the posterior portion of the sella and compressed the hypophysis. The pons was invaded.
28	R. 3,4,5,6	Almost complete destruction of the sphenoid bone.	Rhabdomyoma of nasopharynx. Erosion of bones at base of skull. Extension to right middle cranial fossa and to right cerebello-pontine region. Compression of aqueduct and fourth ventricle with enlargement of third and lateral ventricles. Invasion of sphenoidal sinus, floor of the sella, and hypophysis. Extension to right orbit and right submaxillary region.
29	R. 5,6,7	None taken	Sarcoma of the nasopharynx. Erosion into the base of the skull. Tumor was found all through the petrous portion of the left temporal bone and in the surrounding soft tissues. It did not break into the cranial cavity. Cervical metastases.
30	R. 1,5,7,9	Negative	Sarcoma of the nasopharynx. Tumor pushed into the right antrum and into the sphenoidal sinus, appearing through the right part of the sella turcica. It extended up along the right cartoid artery. It invaded surrounding tissues vigorously.

* Autopsy performed at Hartford Hospital, Hartford, Connecticut by Dr. Kendell.

ses). Pressure on nerves with resulting irritation and ablation phenomena easily explains all of the symptoms noted in the appropriate distribution of the involved cranial nerves. In one instance, case 8, actual invasion of the temporal lobe took place with a resulting agraphia.

SUMMARY

The clinical picture presented in forty-six cases of malignancy of the nasopharynx has been analyzed. An attempt to explain this picture on the basis of the anatomy of the nasopharynx, of the properties of neoplastic growth, and the disturbances created by pressure, obstruction, and destruction, has been made.

BIBLIOGRAPHY

1. GODTFRIEDSON, E. Malignant Nasopharyngeal Tumors. Acta psychiatra et neurologica. Supplementum XXXIX. 1–323, 1944.

THE TREATMENT OF MILIARY TUBERCULOSIS WITH PROMIZOLE*

EDITH M. LINCOLN, SAMUEL STONE AND OLGA R. HOFFMAN

From the Department of Pediatrics, New York University Medical College, and the Chest Clinic of the Children's Medical Service of Bellevue Hospital, New York City

Received for publication July 29, 1947

Within recent years a number of chemical agents have been used in the treatment of tuberculosis. Encouraging results have been reported with the use of promine and diasone (1, 2), but treatment of tuberculosis in adults with promizole has not been reported favorably (3). However, promizole produced very encouraging results in experimental tuberculosis of small animals (4). We were given the opportunity on the Children's Medical Service at Bellevue Hospital to attempt the treatment of tuberculous children with this drug. A preliminary report of this study has already been published (5).

We decided to try promizole first in that form of tuberculosis which has the worst prognosis and treated five successive cases of meningitis with no beneficial effects that could be determined. The children died six to twenty-five days after treatment was initiated and postmortem examination of the brains in two cases showed no demonstrable retardation of the disease.

Acute generalized hematogenous tuberculosis was then selected for treatment with promizole because the course of this disease is more prolonged than that of meningitis thus allowing more time for action of a drug. The prognosis of this form of tuberculosis is almost as serious as that of tuberculous meningitis. Engel (6) saw only one recovery in fifteen years in a large pediatric service. Wallgren (7) reported 84 cases of miliary tuberculosis seen over a period of fifteen years with recovery in five. We have not seen a permanent recovery from acute miliary tuberculosis on the Children's Medical Service of Bellevue Hospital during an observation period of 25 years.

During a period of over 17 years prior to the beginning of this study in June 1944, 102 cases of generalized tuberculosis of miliary or slightly

* Aided by grants from the National Tuberculosis Association and from Parke Davis & Company.

larger size were seen. Death occurred in 88 of these cases within three months after the diagnosis of miliary tuberculosis was established and only three children survived for more than a year. In two of these latter cases the disease progressed slowly until death occurred from meningitis in one case, and from chronic pulmonary tuberculosis in the other. The third case, a negro boy two years old was the only one who showed definite recession of the miliary tubercles on x-ray. He died of acute tuberculous pneumonia and streptococcic pericarditis 23 months after the diagnosis of miliary tuberculosis was first established. On postmortem examination the miliary tubercles in the lungs, liver and spleen were in varying stages of fibrosis, hyalinization and calcification, although some caseous tubercles were present (8).

Every case in this series showed roentgen evidence of mottling throughout both lung fields, and manifest primary tuberculosis was present on x-ray in 91%. In more than 25% of the cases, the development of miliary tuberculosis occurred while the children were under observation for primary tuberculosis. In practically every child fever accompanied, and usually preceded, the appearance of the miliary shadows on x-ray but there was no abrupt change in general condition and nothing but the fever to date the onset of this complication. Moreover in this group, where the time of onset of miliary tuberculosis was known, as well as in our entire group of 102 cases, enlargement of the spleen and of the superficial lymph nodes was not a constant finding occurring in only 60% of the cases later proven by autopsy to have generalized tuberculosis.

Our past experience therefore leads us to believe that miliary pulmonary tuberculosis is a disease of very grave prognosis, that it rarely clears even temporarily and that in children it is almost invariably part of the clinical picture of generalized miliary tuberculosis.

TREATMENT OF ACUTE MILIARY TUBERCULOSIS WITH PROMIZOLE

DOSAGE

In our first cases we gave an initial dose of 1 gm. daily and increased the dosage rapidly to the point of toxicity. In our more recent cases we have begun with 1 gm. daily and increased slowly, checking with the blood levels, until a daily dose up to 5 gms. was reached. We have attempted to achieve a blood level of promizole of 2 to 3 mgms. % since

we secured apparent therapeutic effects at this level. In two of our early patients, acting on the advice of Dr. Medlar, we reduced the dose to 1 gm. daily after treatment for six months with larger doses and in another case the dose was reduced after two months because of leucopenia. It has been possible to maintain adequate blood levels on this low dosage. We plan to diminish the dose in new cases after we have

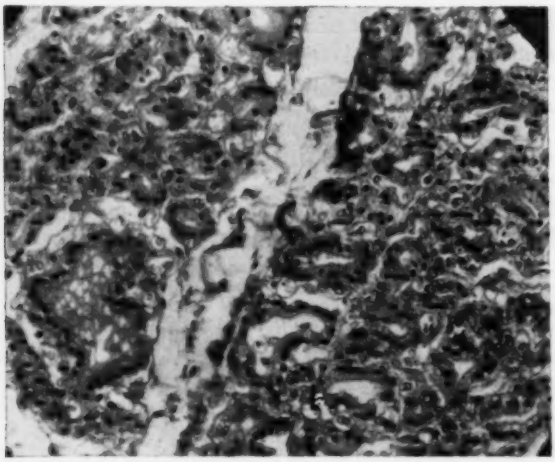


FIG. 1. Thyroid gland of a child who died of miliary tuberculosis after treatment with 43 gms. of promizole during a period of 34 days. Only a rare acinus contains colloid. Tall columnar epithelium lines most of the follicles. Similar changes have been described in guinea pigs treated with promizole.

clinical evidence of the effect of the drug either in diminution of the mottling on x-ray or in toxic effects such as leucopenia.

TOXIC EFFECTS

Vomiting has been severe in only one case and ceased after the drug was temporarily discontinued. The fluid intake of this child had been low and she tolerated the drug well when administration was resumed.

Blood. Leucopenia occurred in two cases after three weeks and after four months of treatment. The lowest white blood cell count was 2,780 with 50% polymorphonuclear cells; after temporary withdrawal of the drug the count rose. One child, after nine days of treat-

ment showed a fall in hemoglobin to 8 gm. per 100 cc. and a red blood cell count of 2,960,000 per cu.mm. Following one transfusion his red

FIG. 2. P. C., Case I, a 2 year old girl, showing enlarged nipples which appeared after 7 months of treatment.

blood cell count and hemoglobin remained within normal limits on continued administration of the drug.

Cyanosis appeared as early as a few hours after the first dose of promizole and was persistent in two children. Methemoglobin was found in the blood by photospectometry even when cyanosis was not noted clinically.

Skin. Vulval pruritis lasting for a week occurred in one case.

Promizole had been discontinued for one week and the symptoms began several hours after the medication was resumed.

Jaundice. One boy with peritonitis and enlarged liver had icteric sclerae and skin and an icterus index of 20 for a week. We can only speculate whether the icterus was due to liver damage from tuberculosis or to the medication.

FIG. 3. R. C., Case II, a 5 year old girl, showing enlargement of breasts after 20 months treatment.

Thyroid Gland. A definite increase in size appeared in all our cases two to five months after the drug was started. Withdrawal of the drug or the administration of desiccated thyroid gland caused marked decrease in size of the gland. This effect of promizole has been previously described (9). On autopsy in animals hyperplasia of the thyroid gland with markedly diminished colloid secretion was reported. One of our cases who died after 34 days of treatment showed a similar reaction in his thyroid gland (Fig. 1). This action of promizole appar-

ently resembled the effect of sulfonamides and thiourea on the thyroid gland (10). In the three cases treated for more than two years, the rate of development of the carpal centers has been within normal limits.

Sex Maturation. The three cases treated for more than two years all showed secondary sex characteristics. The younger girl, Case I, developed enlarged nipples (Fig. 2) and a few labial hairs after seven months of treatment when she was less than three years old. Urine assay at this time showed a slight increase in the excretion of 17 ketosteroids; 1.9 mgms. daily.[1] Case II showed nipple enlargement after twenty months of treatment and her urine assay showed excretion of 3.1 mgms. daily of 17 ketosteroids. The breast tissue in this child at the age of five years is palpable and visible (Fig. 3). The boy has no visible change in his genitalia but pubic hair is present at the age of eight years.

CASES OF ACUTE GENERALIZED MILIARY TUBERCULOSIS TREATED WITH PROMIZOLE

We have treated eleven children with acute miliary tuberculosis with promizole. All showed evidence of primary pulmonary tuberculosis as well as mottling of miliary or slightly larger size throughout both lung fields.

Three of these cases have been treated for less than six months and while all are doing well it is too early to evaluate results of therapy. Three cases were treated for less than a month. These comprise a four months old white boy (W. L.) who died 16 days after treatment was begun; a 16 months old negro boy (R. G.) who was treated intensively for 12 days and then removed from the hospital against advice. This boy is alive two years later in a hospital for tuberculous children and still shows evidence of miliary tuberculosis on x-ray. It is impossible to place his case in either the treated or untreated group. The third case (V. B.) was a white girl four months old treated for 26 days, whose medication was stopped because of a shortage of the drug. She died of tuberculous meningitis, showing the first symptoms five weeks after medication was discontinued.

Five consecutive cases of acute miliary tuberculosis were treated for more than a month. Two of these cases died, one of meningitis

[1] Urine assays for 17 ketosteroids were done by Dr. Konrad Dobriner.

after 4½ months of treatment and the other after receiving promizole for seven weeks. Three children are alive and apparently free from miliary tuberculosis over two years after treatment was begun. A brief summary of the two cases who died follows:

R. L. Porto Rican male was first seen when six months old with a possible pneumonia following mastoidectomy. X-ray revealed a clouding of the right upper lobe and fine mottling throughout both lungs. Miliary tuberculosis was diagnosed

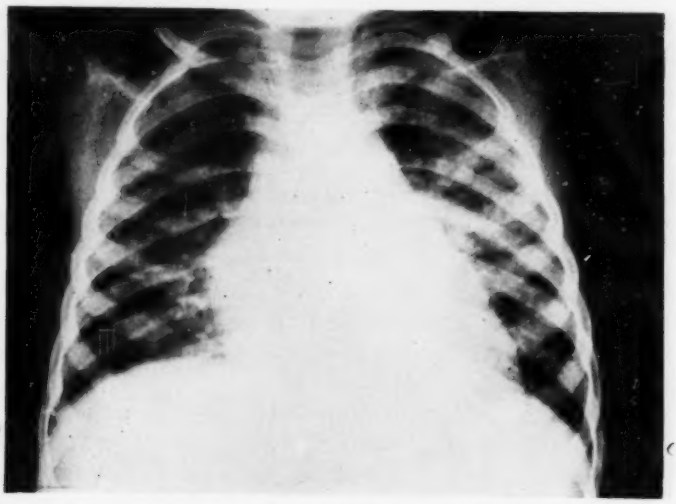


FIG. 4. (A) P. C., Case I. X-ray taken May 1944 shortly before treatment showing mottling throughout both lung fields.

and promizole begun at the age of seven months in dosage of 0.5 gm. daily. The infant at this time weighed 13 lbs. and was acutely ill with high fever and a constant paroxysmal cough. There was some clinical improvement at first, fever was lower and on some days the temperature was normal; anorexia disappeared and there was a small weight gain. But the primary focus and the disseminated mottling increased steadily in size. Fever recurred and the child died after 4½ months of continuous therapy with promizole.

E. B. negro male two years old was admitted to Bellevue Hospital December 1944 with a history of two months illness and x-ray evidence of miliary tuberculosis and primary pulmonary tuberculosis. On admission his temperature ranged from 102°F. to 104°F. daily, he was acutely ill, and had a paroxysmal cough. His liver was felt almost at the level of the umbilicus and the spleen was palpable. One

gram promizole daily was first given December 19 and increased to two grams daily by January 10, 1945. Medication was suspended January 13, 1945 because of extreme distension but started again on January 24 and continued until death on February 9. Serial x-rays showed progressive increase in size of the hematogenous tubercles and cavitation in the primary focus. Autopsy revealed caseous primary tuberculosis and tuberculous pneumonia and empyema, miliary tuberculosis of lungs, liver, spleen, kidney and pericardium and early tuberculous menin-

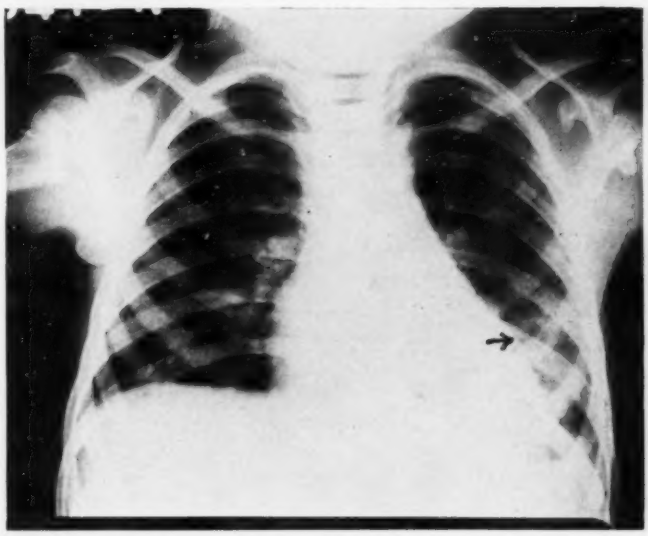


FIG. 4. (B) P. C., Case I. X-ray taken March 1946 showing marked clearing of miliary shadows, although the primary focus is still visible in the third and fourth left interspaces. Note the annular shadow in the third interspace interpreted as a cavity.

gitis. The thyroid gland was normal in size but on microscopic examination showed an almost complete absence of colloid and other changes similar to those described by Feldman (4) in guinea pigs treated with promizole (Fig. 1).

The three cases who have survived acute miliary tuberculosis are reported in greater detail:

Case I. P. C. negro girl was admitted February 1944 at the age of two years with an excavating primary tuberculosis of the left lower lobe and miliary seeding throughout both lungs (Fig. 4-A). Irregular fever to 102°F. was present for a

month before admission and for five weeks after entering the hospital. She had lost weight but was in fair condition, weighing 22 lbs. and did not look ill. The liver was felt two finger breadths below the costal margin; the spleen was not palpable. There was a general slight enlargement of the superficial nodes. During the 3½ months following admission her general condition improved and she gained weight. Erythrocyte sedimentation rate fell from 28 mm. in an hour to 14 mm. (Cutler Method) and white blood cell count from 20,000 to 12,000. However, the mottling on x-ray became larger, the primary cavity more definite and

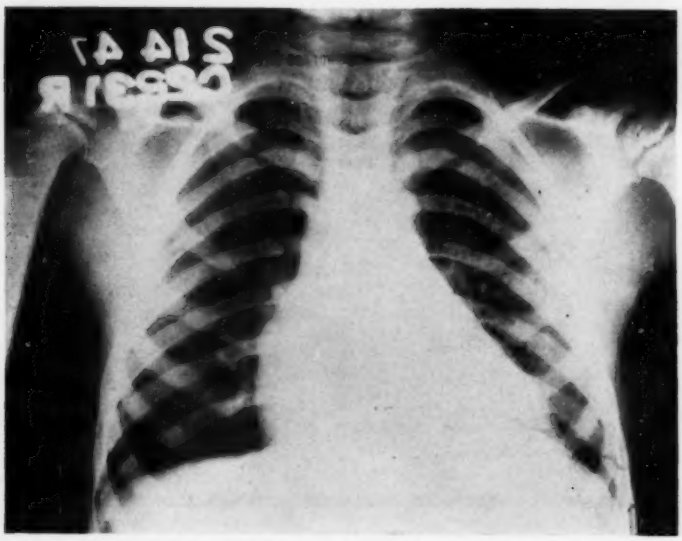


FIG. 4. (C) P. C., Case I. X-ray taken February 1947, showing clear lung fields except for faint clouding in third and fourth left interspaces, remains of primary focus.

her spleen became palpable. Promizole 3 gms. daily was started after 3½ months of observation on June 6, 1944. Ten weeks later in August 1944 the mottlings on x-rays first appeared smaller. In October she had a fever of 102°F. and diminished breath sounds with moist rales were found over the left chest posteriorly. X-ray showed an extension of the primary lesion and shortly after this acid fast bacilli were found in the gastric contents for the first and only time. The dose of promizole was increased to 4 gms. daily. In November the miliary lesions were less evident on x-ray and by January 1945 the mottling was barely visible, the rales had disappeared and the spleen was no longer palpable. The cavity in the primary focus was last seen on August 30, 1946 (Fig. 4-B). At the present time there is still a

faint area of clouding at the site of the primary lesion and small calcifications are visible at the base of the left lung and in the spleen, but no mottling is visible in the lung fields (Fig. 4-C). This child has to remain in the hospital for social reasons but is now apparently well three years after the onset of miliary tuberculosis.

Case II. R. C. negro girl was admitted in May 1944 at the age of four years with an extensive excavating primary tuberculosis of the left upper lobe and with mottling of miliary size throughout both lungs (Fig. 5-A). She had been ill with

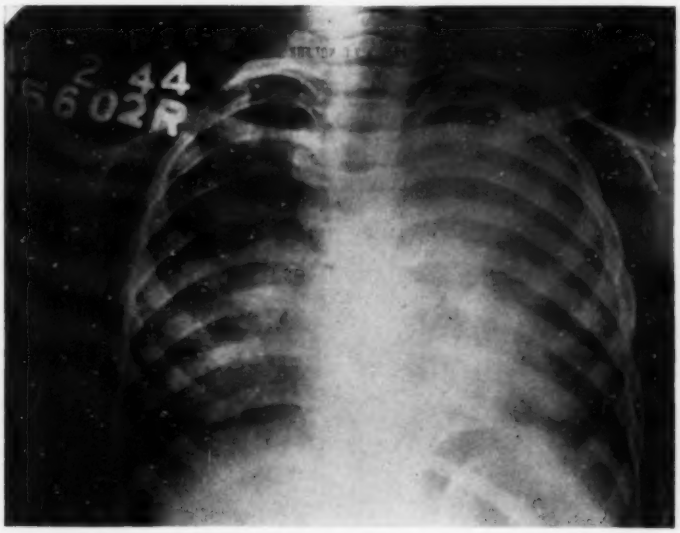


FIG. 5. (A) R. C., Case II. X-ray taken June 1944 before treatment, showing clouding in left lung to second rib, with enlargement of right root and mediastinum widened to right. Mottling of miliary size is seen throughout rest of both lung fields.

an irregular temperature to 103°F. for two months before admission but did not look acutely ill on admission and was well nourished, weighing 39 lbs. Dullness and inconstant moist rales were heard over the left upper anterior lung field. The liver edge was one finger breadth below the costal margin, the spleen was easily palpable and there was general enlargement of the superficial lymph nodes. Promizole 3 gms. daily was begun on June 6, 1944. Within 24 hours she began to vomit, cyanosis was noted and on June 12 promizole was stopped because of delirium and choreiform movements of the extremities. After this condition subsided, administration of promizole was resumed with 2 gms. daily and later the dosage was increased to 2½ gms. There was no return of symptoms of toxemia. Six weeks

after beginning promizole there was roentgen evidence of increase in size of the primary focus with definite cavitation. The mottlings also appeared larger at this time. The temperature now remained below 101 and the child began to gain weight. The mottling on x-ray first appeared smaller in October 1944, 4½ months after treatment was initiated, although the primary focus remained unchanged and acid fast bacilli were recovered at this time from the gastric contents. At this time the red blood cell count was 3,000,000 per cu.mm. and the white blood cell count reached 3,800 per cu.mm. in November. Promizole was discontinued for about a month and then 1 gm. daily was begun in December and this dose has been

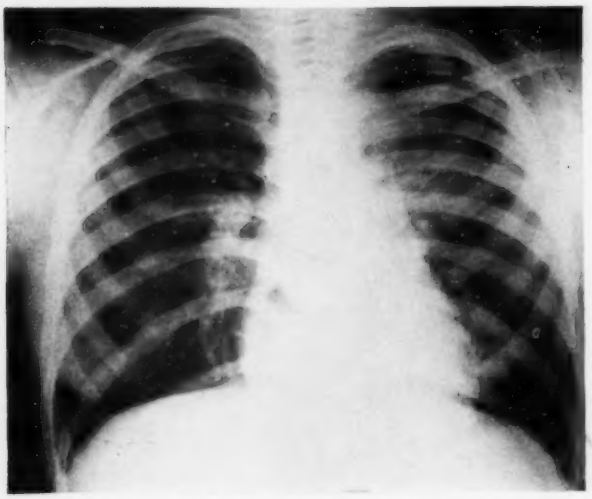


FIG. 5. (B) R. C., Case II. X-ray taken June 1946 after two years treatment with promizole, showing clear lung fields except for clouding in second left interpace continuous with root, interpreted as remains of primary focus.

continued to date and the blood count has remained normal. The area of clouding in the left upper lobe had diminished markedly by April 1945 and the miliary seeding was barely visible, the cavity had disappeared and no rales could be heard. The spleen was just palpable and the temperature was normal except for a very occasional rise to 100.5°F. The child was sent home and has remained well. Since January 1946 no mottling has been visible on x-ray (Fig. 5-B). In January 1947 a faint clouding in the second left interspace and a moderate widening of the mediastinal shadow to the left were the only pathological roentgen findings.

Case III. J. A. a Porto Rican boy six years old was admitted to Bellevue Hospital on August 31, 1944. The first diagnosis of miliary tuberculosis had been made three months previously when he had high fever, enlarged liver and spleen,

a positive tuberculin test and x-ray evidence of mottling throughout both lung fields in addition to enlarged right bronchopulmonary nodes (Fig. 6-A). Two weeks prior to transfer to Bellevue he had developed a pleural effusion on the right side which was subsiding at the time of admission. Within the first month at Bellevue he developed a left sided pleural effusion and following this, abdominal tenderness with marked enlargement of liver and spleen. Promizole was started on October 14, 1944 in dosage of 3 gms. daily. He vomited at intervals, was

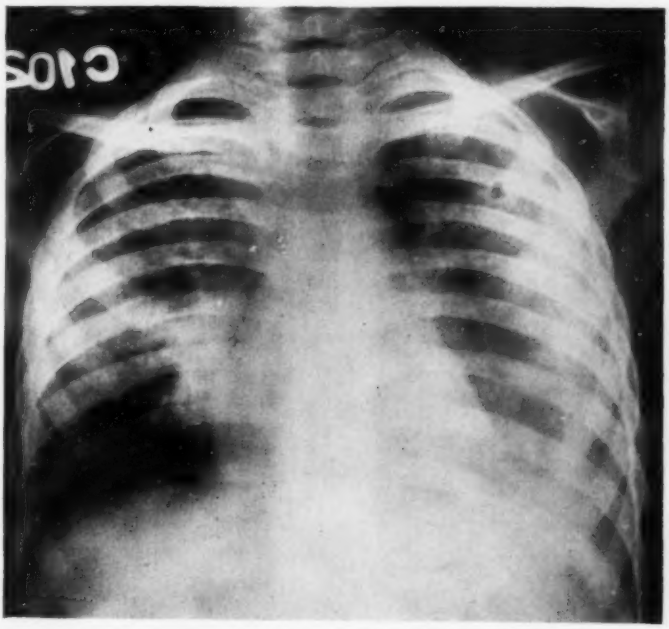


FIG. 6. (A) J. A., Case III. X-ray taken October 1944 before treatment showing left pleural effusion, enlarged right root and mottling of miliary size throughout both lungs.

cyanotic and dyspneic, and lay constantly with his knees flexed. Promizole was discontinued after 23 days because the white blood cells were only 3,800 per cu.mm. but was begun again in 1 gm. dosage after an interval of a month and has been continued to date. The abdominal symptoms disappeared after one month but there was at the same time an increase in the mottling on x-ray. In addition, culture of the urine on December 5, 1944 showed tubercle bacilli after microscopic examination of urine constantly showed a few white blood cells. The positive urine cultures continued for ten months although retrograde pyelograms were

normal. Urine cultures have been negative since October 1945 although white blood cells continue to be present in the sediment. In March 1945 a diagnosis of tuberculous spondylitis of the 11th and 12th dorsal vertebrae was made and at this time acid fast bacilli were found in the gastric contents. In August 1945 a bilateral chorioretinitis was discovered, the eyegrounds having been negative in March. At the present time this boy is in fair condition awaiting surgical fusion of his spine. X-rays of his lungs have shown an entirely clear parenchyma since October 1945 (Fig. 6-B) and there is evidence of calcification in the spleen (Fig. 6-C).

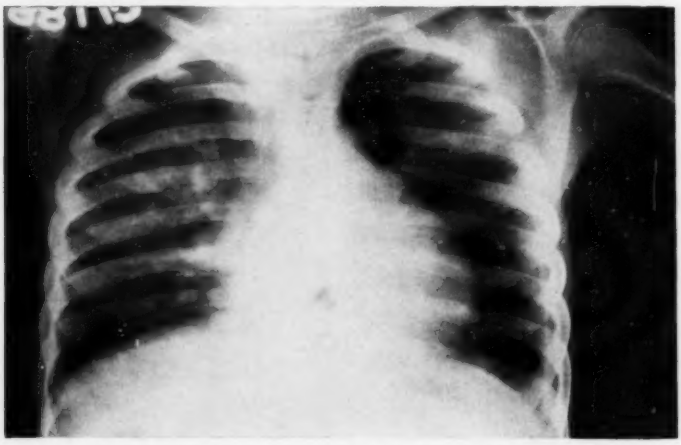


FIG. 6. (B) J. A., Case III. X-ray taken October 1946 after two years treatment with promizole showing thickening of left axillary pleura and slight enlargement of right root. The miliary mottling has completely disappeared.

Encouraged by our results in acute miliary tuberculosis we are now using promizole in other forms of tuberculosis of hematogenous origin. It is too early to report fully on our results, but we should like to report the result of treatment of one individual with chronic hematogenous tuberculosis who developed pulmonary miliary tuberculosis. The prognosis of this form of hematogenous tuberculosis is apparently not as serious as that of acute generalized miliary tuberculosis (Miller, 11).

Case IV. F. S. was first seen because of obvious hematogenous tuberculosis. In April 1944 at the age of eleven following an operation for a supposed thyroglossal cyst which proved to be a tuberculous lymph node, she developed dactylitis of hand and feet and in July 1944 a left sided pleurisy with effusion. Clouding of

both apices appeared in March 1945 and a pleurisy with a small effusion on the right in December 1945. Mottling of miliary size was first definitely seen in March 1946. In April a choroiditis was first noted. By June the mottling in the

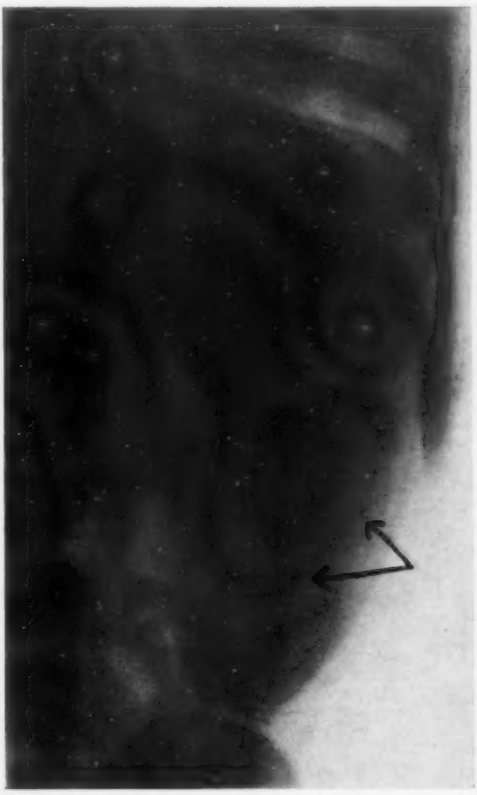


FIG. 6. (C) J. A., Case III. X-ray taken in 1946 showing calcifications within enlarged spleen.

lung fields had become very marked (Fig. 7-A). Physical examination at this time revealed a poorly nourished girl with dullness and diminished breath sounds at left base posteriorly. For the first time moist post tussic rales were heard over both apices. Liver and spleen were not palpable, there was enlargement of superficial lymph nodes. Promizole was started on June 22, 1946 and the dose increased to 4 gms. daily. The patient continued to receive this amount of the drug with

no evidence of toxicity. Shortly after treatment was begun tuberculosis of the right sacro iliac joint was diagnosed. There has been marked general improvement including a weight gain of 7½ lbs. X-ray seven weeks after treatment was

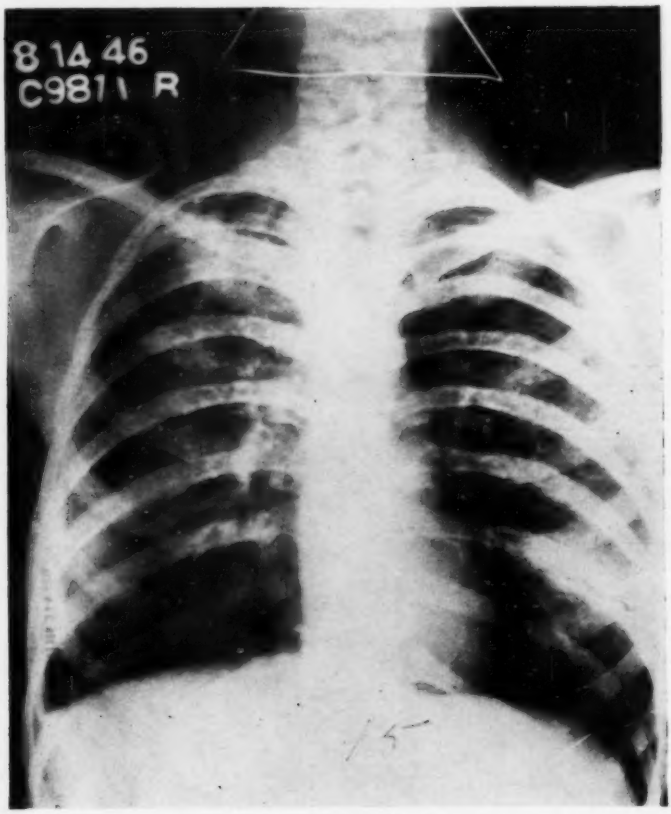


FIG. 7. (A) F. S., Case IV. X-ray taken 8/14/46 six weeks after treatment with promizole was begun, showing miliary mottling in both lung fields.

begun shows no change but by December 23, 1946, (Fig. 7-B) six months after promizole was first begun, there is marked roentgen evidence of clearing and on March 28, 1947 no roentgen evidence of miliary tuberculosis can be found (Fig. 7-C).

DISCUSSION

All the evidence we have gathered tends to show that promizole acts slowly in the child and that its effect on tuberculosis of hematogen-

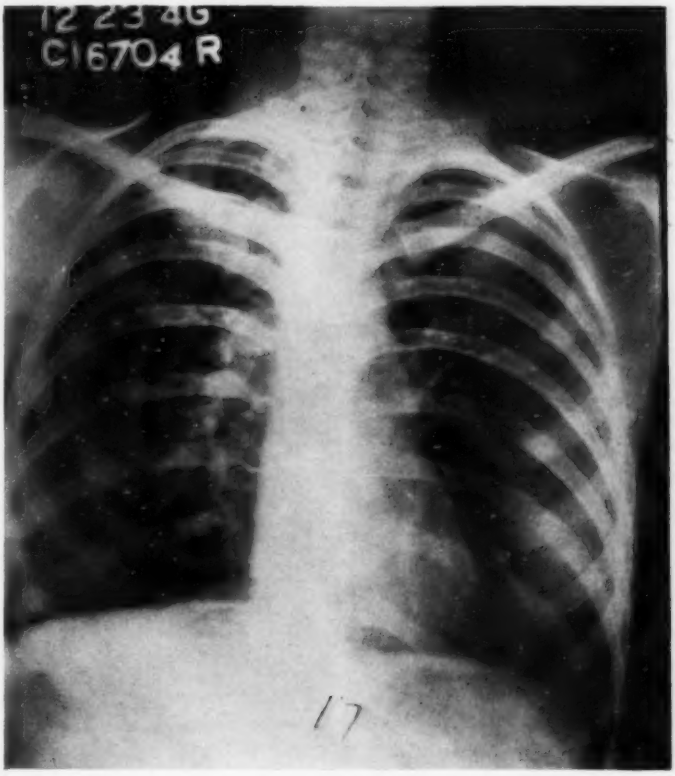


FIG. 7. (B) F. S., Case IV. X-ray after six months of promizole therapy (Dec. 1946) showing marked diminution in extent of miliary tuberculosis.

ous origin is slower than the results reported of antibiotics such as streptomycin. In the four cases where we have roentgen evidence of complete clearing of miliary tuberculosis, the mottling did not begin to diminish until ten to eighteen weeks after promizole was first ad-

ministered. We have earlier proof of bodily response to the drug in evidence of its goitrogenic action. While enlargement of the thyroid is usually first observed two to five months after promizole is first

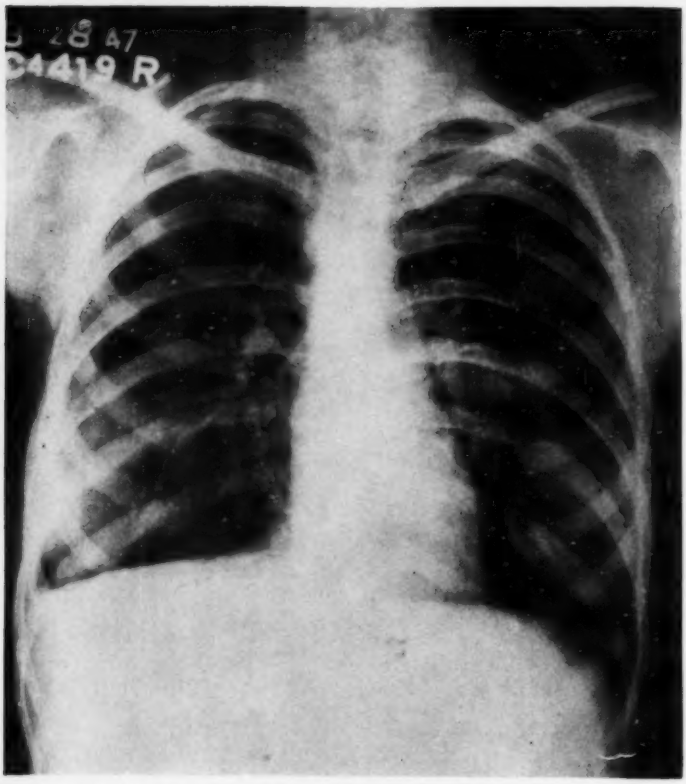


FIG. 7. (C) F. S., Case IV. X-ray taken March 1947 showing complete clearing of miliary tuberculosis after nine months of therapy.

given, we have pathological evidence of the goitrogenic action of promizole in the case who died 43 days after beginning treatment (Fig. 1).

Since most individuals with acute generalized miliary tuberculosis die within three months after first roentgen evidence of the disease, it

is obvious that we can not hope to arrest all cases of miliary tuberculosis with promizole. Chronic miliary tuberculosis lasting more than three months apparently has a better prognosis than the acute forms. Hoyle and Veazey (12) reported that 25% of individuals, usually adolescents or young adults, with chronic miliary tuberculosis go on to arrest of their disease. VanCreveld and Huet (13) reported 13 cases of recovery from chronic miliary tuberculosis during an observation period of 16 years. While we have never seen spontaneous recovery from miliary tuberculosis in children even where the disease became chronic both Engel and Wallgren have reported instances of recovery. We may speculate that an individual with miliary tuberculosis who survives the usual duration of three months shows more natural resistance.

The first five cases of acute generalized miliary tuberculosis treated for more than a month were consecutive cases. It is suggestive that the two cases who died were diagnosed only three weeks and one month before treatment was begun, whereas two of the three cases who have ultimately shown complete roentgen clearing had been diagnosed $3\frac{1}{2}$ to $4\frac{1}{2}$ months before treatment was initiated.

Our group of cases is small but in view of our past experience with miliary tuberculosis we feel that the evidence is striking that promizole may have a favorable action in suitable cases of miliary tuberculosis. In our next group of cases we plan to combine promizole with streptomycin in the treatment of miliary tuberculosis. Thus we hope to avail ourselves temporarily of the rapid action of streptomycin and then continue the treatment with promizole which has the great advantage of ease of administration, relative lack of toxicity and which can apparently be given safely and effectively over a period of years.

SUMMARY

Promizole has been used in the treatment of miliary tuberculosis in children. Five consecutive cases of acute generalized miliary tuberculosis were apparently adequately treated with promizole.

Of these, two children died 43 days and $4\frac{1}{2}$ months after therapy was begun.

Three children showed complete recession of roentgen evidence of miliary tuberculosis and are alive 30 to 33 months after promizole was

first given. In these cases who survived acute miliary tuberculosis the primary pulmonary lesions cleared slowly and in two cases went on to cavitation. In one case roentgen evidence of the primary focus is still present. One child developed tuberculosis of the spine, choroiditis and positive urine cultures for tubercle bacilli while taking the drug. All three cases are still receiving maintenance doses of promizole.

One adolescent girl is reported who developed acute miliary pulmonary tuberculosis in the course of a chronic protracted hematogenous tuberculosis. The miliary lesions have disappeared while under treatment with promizole.

Promizole is goitrogenic and has a stimulating effect on secondary sex characteristics, causing enlargement of nipples and breast tissue and growth of pubic hair. No toxic effects were observed which would require permanent discontinuance of the drug. No irreversible toxic effects have been observed with the possible exception of the effect on sex maturation.

REFERENCES

1. Hinshaw, H. C., Pfuetze, K. H., and Feldman, W. H.: Treatment of Tuberculosis with promin: A progress report. Am. Rev. Tuberc., 1943, **47,** 26.
2. Petter, C. K. and Prenzlau, W. S.: Treatment of tuberculosis with diasone. Am. Rev. Tuberc., 1944, **49,** 308.
3. Feldman, W. H., Hinshaw, H. C., and Pfuetze, K. H: Present status of chemotherapy in tuberculosis. Ann. Int. Med., 1945, **22,** 696.
4. Feldman, W. H., Hinshaw, H. C., and Mann, F. C.: The effect on previously established tuberculosis of guinea pigs of 4,2′-diaminophenyl-5′-thiazolylsulfone (promizole). Am. Rev. Tuberc., 1944, **50,** 418.
5. Milgram, L., Levitt, I., and Unna, M.: Promizole treatment of miliary tuberculosis. Am. Rev. Tuberc., 1947, **55,** 144.
6. Engel, S.: Meningitis tuberkulose and Miliartuberkulose, in Engel, S., and Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, Volume I, p. 576.
7. Miller, J. A. and Wallgren, A.: Pulmonary Tuberculosis in Adults and Children. New York, Thomas Nelson & Sons, 1939.
8. Lincoln, E. M.: Hematogenous tuberculosis in children. Am. J. Dis. Child., 1935, **50,** 84.
9. Higgins, G. M. and Larson, R. A.: Hyperplasia of the Thyroid Gland induced by 4,2′-diaminophenyl-5′-thiazolesulfone (promizole). Proc. Staff Meet., Mayo Clin., 1944, **19,** 137.

10. MacKenzie, C. G. and MacKenzie, J. B.: Effect of sulfonamides and thiourea on the thyroid gland and basal metabolism. Endocrinology, 1943, **32,** 185.
11. Miller, J. A.: Hematogenous pulmonary tuberculosis. Am. Rev. Tuberc., 1934, **29,** 489.
12. Hoyle, J. C. and Vaizey, J. M.: Chronic Miliary Tuberculosis. London, Oxford University Press, 1937.
13. VanCreveld, S. and Huët, G. J.: Chronic Miliary Tuberculosis. Acta Med. Scandinav., 1943, **113,** 135.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

Cambridge Medical History. By SIR WALTER LANGDON-BROWN. 119 pp. Cambridge University Press, New York, New York, 1947.

In this delightful little book, Sir Walter Langdon-Brown describes the history of medicine in Cambridge in a series of seven biographical essays. These portray the work and personalities of such men as Caius, Gilbert, Glisson, Heberden, Hartley, Haviland, Paget, Humphry, Foster, and Allbutt. The book is well written and a worthy addition to items on medical history. It will interest all who have studied at Cambridge, as well as others interested in the particular personalities portrayed.

H. N. H.

Clinical Radiology. A Correlation of Clinical and Roentgenological Findings. Edited by GEORGE UTLEY PILLMORE. 2 vols. Illus. 1600 pp. $45.00. F. A. Davis Co., Philadelphia, Pennsylvania, 1946.

This two volume work written by fifty-eight contributors has attempted to present the manifold phases of diagnostic roentgenology and their application to clinical problems. The manuscript has been divided into ten parts and includes sections discussing the cardiovascular system, the respiratory system, the gastro-intestinal system, the urogenital system and the osseous system. Sections are also devoted to the brain, spinal cord and nasal accessory sinuses. Small chapters are also given to a consideration of soft tissue roentgenology and to the localizing of foreign bodies by roentgenographic methods.

Although there are several minor omissions, this work is unusually complete and brings together much of the fundamental knowledge in the field of diagnostic roentgenology. Like any work that is written by a number of authors, some sections of the manuscript are noticeably better than others. Sections devoted to cardiovascular disease and to intracranial lesions are particularly well done, and, in the case of the former, reflect the wide experience of the section's author in some of the more recent technical methods that have been developed. The section on the respiratory system is disproportionately large, and, as a result, some of the material is redundant. For example, in the discussion of pulmonary tuberculosis, the author presents several classifications of the disease which the average reader will find of very little use. Also, in this section, no reference is made to the place of histoplasmosis in the differential diagnosis of pulmonary calcification. Other omissions in this book are evident principally in the bibliographies which appear at the end of each section. Practically no reference is made to work performed outside of the United States; also, in this country, no reference has been made in the section on the gastro-intestinal system to the classical writings of Templeton.

In general, the format of the book is good. The printing is clear and the manuscript is well bound. The roentgenographic reproductions also are somewhat better than average, although, in a number of instances, the reproductions do not present the opacities in the same relationship as they were in the original films. However, in spite of its shortcomings, this work should be found valuable by students of diagnostic roentgenology and, in particular, by physicians who wish to have at hand a generally complete treatise on the various phases of diagnostic roentgenology.

R. H. M.

Curare, Its History, Nature, and Clinical Use. By A. R. McIntyre. Illus. 240 pp. $5.00. The University of Chicago Press, Chicago, Illinois, 1947.

This monograph, by an author long active in investigation of the properties of curare, furnishes a most useful compilation of scattered information which has been gathered since Claude Bernard first described accurately the action of curare. The first chapters are devoted to a scholarly review of accounts of early explorers of the South American continent, regarding observations on the sources, preparation, and use of curare by the native Indians. Then there is a full section on the botanical characteristics of the various curariform plants. The remainder is devoted to the functional inter-relationships of curare, curarising and decurarising agents, and the host of substances which affect neuromuscular function. This section of the monograph cites almost all of the observations of many investigators; however, no clear principles of function result. Perhaps, owing to the fragmentary nature of our knowledge of underlying mechanisms in this field, no clearer analysis is possible at this time.

J. L. L., Jr.

Dynamic Aspects of Biochemistry. By Ernest Baldwin. Illus. 457 pp. 21 s. net. University Press, Combridge, England, 1947.

Here is the type of biochemistry book of which more are needed. Many scientific workers in various fields seek an exposition of biochemistry which does not emphasize the more or less straight-forward, general, textbook background on the one hand, nor delves deeply and exclusively into one narrow field on the other. Rather there is wanted a broad discussion of the more fluid and detailed aspects of a number of biochemical subjects integrated into the outlines of biology as a whole. This book is a big contribution in this direction.

Under the general heading of "Enzymes", there are taken up as successive chapters, "The General Behaviour and Properties of Enzymes", "The Nature of the Catalytic Process", "Hydrolases and Phosphorylases", "Oxidizing Enzymes", and "Other Enzymes". Under the general heading of "Metabolism", the author discusses, "Methods Employed in the Investigation of Intermediary Metabolism", "Food, Digestion and Absorption", "General Metabolism of Proteins and Amino-Acids", "Special Metabolism of the Amino-Acids", "Excretory Metabolism of Proteins and Amino-Acids", "Some Special Aspects of Nitrogen Metabolism",

"Metabolism of Purine Derivatives", "Anaerobic Metabolism of Carbohydrates, Alcoholic Fermentation", "Anaerobic Metabolism of Carbohydrates, Muscle and Liver", "Aerobic Metabolism of Carbohydrates", and "Metabolism of Fats".

The book is well integrated and written in an easy, conversational style. Historical background is woven into the general discussion at the appropriate place, not taken up as a separate section. The same is true of the more usual factual background which is brought in.

Attention is paid to the development of our concepts of biochemical physiology and not just to fact. Some of the thoughts developed by the author are quite challenging, such as: "In view of these considerations, we must inquire whether we have perhaps been led astray by studying muscle metabolism only under anaerobic conditions, and whether anaerobic contraction has any real biological significance at all." In the discussion of purine metabolism, little is said about more recent knowledge of sources of carbon and nitrogen in these substances.

The book is to be highly recommended and can be read through to advantage and with sustained interest. It is also an excellent reference work on general topics. It is to be hoped that more books of this type will appear.

F. W. B., Jr.

Experiences with Folic Acid. By Tom D. Spies. Illus. 110 pp. $3.75. The Year Book Publishers, Inc., Chicago, Illinois, 1947.

The author's remarks are based on a most extensive clinical experience with folic acid therapy. Observations are reported on 218 cases. Some of the hematological responses among cases of Addisonian pernicious anemia, tropical sprue, nutritional macrocytic anemia, and cirrhosis of the liver were dramatic. The last group of patients is most worthy of note. There are presented the basic structural formulae of compounds with which clinical and laboratory investigations are being made. This is a book worthy of an evening's perusal. However, it does not emphasize that present clinical experience indicates folic acid therapy in pernicious anemia, in our present state of knowledge, may be very dangerous. Severe, sudden, and frequent neurological relapses occur in an unpredictable manner.

P. W.

Operative Gynecology. By Richard W. TeLinde. Illus. 751 pp. $18.00. J. B. Lippincott Company, Philadelphia, Pennsylvania, 1946.

Doctor TeLinde's book on operative gynecology is a valuable addition to gynecological literature. It consists of 751 pages and covers the whole field of the surgical treatment of gynecological disorders. The subject matter is divided into thirty-eight chapters and is well presented. There are 324 illustrations and an excellent index.

Because of its completeness and the excellence of its illustrations, this volume cannot help being useful to practicing surgeons as well as to internes and house officers. The author stresses not only operative technic and surgical principles,

but also the role of nonoperative therapy in many gynecological disorders. The indications and methods of irradiation therapy are also well presented. In general, therefore, after reading this book carefully from cover to cover, this reviewer closes it with appreciation of its excellence and feels certain that it will find wide acceptance.

L. R. W.

Parenteral Alimentation in Surgery, By ROBERT ELMAN. 267 pp. $4.50. Paul B. Hoeber, Inc., New York, New York, 1947.

This volume, which represents a full length presentation of the entire problem, was originally awarded the quinquennial Samuel D. Gross prize of the Philadelphia Academy of Surgery. It is a monograph of 267 pages carefully and simply written, carrying tables, figures, and references which serve to amplify well the text. While much of the basic material is known to all who have kept abreast of advances in parenteral therapy, the reader is easily led into the more technical aspects as each chapter unfolds its own special subject matter. A consideration of water and electrolyte needs, of caloric needs, and vitamin needs precedes the more-emphasized consideration of protein needs. The author, a well recognized authority, then discusses plasma and whole blood transfusions, pure amino-acids vs. hydrolyzed protein and the many related problems of their preparation and use. Finally, a practical program for parenteral alimentation is offered. Dealing effectively and simply with one of the frontiers of clinical surgery, this volume represents a source of well compiled information to which clinicians and investigators should frequently turn.

S. McL.